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# CONTENTS

Genic and Hormonal Factors in Biological Processes . . 359
*C. H. Danforth*

Clinical and Pathological Aspects of Acute Leukemia . . 377
*Claude E. Forkner*

Chronic Gastritis: Clinical Aspects . . . . . 392
*Burrill B. Crohn*

Vitamin A with Special Reference to Therapy . . . . 406
*Arthur M. Yudkin*

Recent Accessions to the Library . . . . . 418

In Memoriam, William Hallock Park . . . . . 420

Deaths of Fellows . . . . . 422

Twelfth Graduate Fortnight . . . . . 424

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IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JUNE 1939

# GENIC AND HORMONAL FACTORS IN BIOLOGICAL PROCESSES

*Harvey Lecture, April 20, 1939*

C. H. DANFORTH

DURING the last forty years biologists in increasingly large numbers have been turning their attention to genetics, and during the last thirty years other biologists, also in increasing numbers, have been concentrating on the endocrines, so that at the present time one or the other of these phases of the subject is of prime interest to a large proportion of students of biology and scientific medicine. But the methods, and frequently the materials, employed by the two groups are so different that the number of investigators who have interested themselves and are well-informed in both fields remains relatively small.

It is not surprising that seeming inconsistencies have arisen, but it is a part of our scientific faith that real inconsistencies do not exist, and argument over heredity vs. environment or genes vs. hormones is useful only insofar as it tends to clarify the nature of factors or processes which are interdependent and mutually indispensable. With the diversity of approach as great as it is, it becomes incumbent upon us to attempt from time to time to clarify and evaluate not merely our own findings but those that have been obtained by different means and by other investigators,

in order that we may have a clearer and more harmonious view of the whole.

Since the time of Darwin it has been customary to look at biological problems phylogenetically, with the result that in his reflective moments the biologist feels a little uncomfortable if he cannot postulate some way in which the structures or reactions in which he is interested might perhaps have been evolved. This phase of the subject rarely permits of exact analysis, and reflections upon it are likely to be in a measure unsatisfactory and pre-eminently tentative. Nevertheless the craving for a working hypothesis constantly besets us and may perhaps, with due caution, be indulged at times. To this end it may be expedient to consider, insofar as limitations will permit, a few general implications of recent findings and in the light of these attempt to interpret some of our data relating to secondary sex characteristics.

It is obvious that no one can adequately summarize or properly relate material in fields so vast as endocrinology and genetics. These subjects do not stand out by themselves as two sharply defined domains of science, but have contacts with and transitions into such other fields as those of nutrition, biochemistry and experimental embryology. For the present purpose let us glance first at the genes, hormones and organizers; then consider some evidence bearing on the evolution of sex; and finally attempt to synthesize a point of view with reference to a particular problem, the significance and regulation of sex differences. It may be stated at once that the sequence of presentation is by no means the sequence in which the data and conclusions were developed.

## The Genes

What is frequently referred to as "Mendel's First Law" is still the corner-stone of genetics. Indeed, the basic phenomenon of genetics is believed to be the independence and discreteness of the individual gene. Reproducing itself precisely, except for rare mutations, the gene is in effect "immortal" in the Weismannian sense. Though it may be associated in succeeding generations with various allels, it is not contaminated by them and always emerges from each new combination as pure as an atom released by the breakdown of a chemical compound. While most geneticists doubt if any gene has actually been rendered visible, and some think the nature of the gene is such that it never can be seen, an immense amount of evidence on the position and function of various

*loci* in the chromosomes has been accumulated and there is fair agreement on fundamental concepts of segregation, linkage and other now familiar genetic phenomena which were scarcely dreamt of in the earlier years of genetic study (Darlington[1], Dobzhansky[2]).

One especially important respect in which genetic concepts have undergone a distinct evolution relates to the effect of the genes on somatic traits. It is no longer customary to think of genes as forming a kind of microcosm which mirrors in a way the adult organism (as did the germs envisioned by some of the preformationists). On the contrary, the tendency now is to think of the whole complex as functioning together, but with some genes more important than others in effecting the production of any individual trait. The late Doctor Calvin Bridges illustrated this point graphically by drawing an analogy to a weighing balance, so set that it would tip when all of a certain number of weights of various sizes had been added to one of the pans. The scale would respond only when the last weight, no matter which it might be, was added, and yet the last weight need be intrinsically of no more importance than any of the others. One cannot speak of *the* gene for a particular trait except in the sense that the gene in question is the differentiator in the production of that trait. Under other conditions the seemingly significant gene for the same trait might be an entirely different one.

How the genes exert their influence is still problematical. They are surrounded and maintained by the cytoplasm, which they in turn affect, apparently in two ways. They determine, or at least influence, the reactivity of cytoplasm to both internal and external stimuli and at the same time themselves furnish part of those stimuli. Occasionally cytoplasm may early acquire properties which persist throughout life (Boycott *et al*[3]., Goldschmidt[4]), and possibly for even more than a generation. There is a suggestion, coming from hybridization followed by repeated back crosses, and from polyploids in plants (von Wettstein[5]) that normal morphology is at times conditioned by a certain concordance between genes and cytoplasm. In this, one might perhaps detect a hint that reactivity to genes, even to a particular gene, may have been a matter of gradual cytoplasmic adjustment or evolution, but as yet evidence from such animals as Drosophila and pheasants gives little obvious support to this idea. Even so, it is doubtful if all cytoplasm is equally responsive to all genes. Indeed, one might conceive embryological differentiation to be due to a progressive acquisition by the cytoplasm of a capacity for

reacting with genes to which it had previously been unresponsive. Presumably the same genes are present in all of the cells at all of the stages in the history of each individual; but some of these genes become effective only when the cytoplasm has passed through certain preliminary phases. Perhaps even at the cellular level there is some kind of analogy between the processes of ontogeny and phylogeny.

Whatever the evolutionary sequences may have been, it would seem proper to regard the relations we now find between cytoplasm and genes as a kind of functional symbiosis. The actual anatomical and physiological reactions are essentially cytoplasmic but, as has been abundantly shown, the behavior of the cytoplasm is conditioned by the genes which are associated with it at the moment or have recently been so associated. That this adjustment has come about through evolutionary processes going on within the cell now seems probable.

## The Hormones

The early concept of a hormone as a substance produced by the cells of one part of the body and effective on those of another part is still acceptable. But to refer to hormones as chemical messengers is perhaps a little more figurative than our present concepts should permit. The hormones are usually thought of, justly no doubt, as activators or stimulators, but it is important to remember that they produce their final effects only through such protoplasm as will respond to them. They do not stimulate inanimate matter and, as will be pointed out presently, a hormone may have a very different effect on the same tissue of related species, or even individuals, and on different tissues of the same species or individual. The specificity of most of the hormone-tissue reactions is apparently more properly an attribute of the tissue than of the hormone. It seems to be largely a question of whether or not the tissue will utilize the hormone if it is available. With reference to the prevailing concepts this is perhaps stating the case backwards, but it may contribute something to clarity if we occasionally look at the matter from the less familiar angle.

From this point of view each hormone appears as just another component of the total environment to which all of the cells are subjected. That the hormones may in some measure permanently influence or condition the cytoplasm in a manner analogous to that in which the genes do, is suggested by embryological and experimental findings (Stockard[6]). But on the whole their effects seem to be, if sometimes scarcely

less profound, at least generally more transient than those of the genes. That one hormone or another is absolutely essential to the normal realization of many biological functions[7] is abundantly indicated by an immense amount of published evidence too familiar to call for comment. It is also known that chemically similar substances, and also some synthetic products which may not be actually identical with true hormones at all, can be made to serve adequately in their place. To an evolutionist this presents a challenging problem. What is the significance of the hormones phylogenetically? In attempting to answer this question it is doubtful if one should limit himself to the hormones alone.

Until rather recently we have been inclined to think of the hormones as more or less peculiar to vertebrates, and especially distinctive of mammals. Moreover, we have been possibly a little too much disposed to draw sharp lines of demarcation between hormones and vitamins, and between both of them and simple chemical and physical factors on the one hand and genic influences on the other. Of late the barriers seem to be breaking down. Even in insects, hormones are now receiving much attention (Beadle and Ephrussi[8], Kühn[9], Wigglesworth[10]). It appears that in certain species of insects a single hormone effective on some of the tissues is produced by several different organs, each with its own primary function. In other species, where its function, if any, is unknown, this same hormone may still be produced in significant amounts. One might suspect that the appearance of a hormone may ante-date phylogenetically any adaptation of the tissues for its use.

## Organizers and Vitamins

The popular tendency that would attribute directive or creative powers to hormones has been carried to an extreme with reference to organizers. The very word suggests active determination, but it would seem that here again there is a disposition to mistake the passive means for the active agent. Organizers, like hormones, seem to be only components, albeit essential ones, in the environment of normally developing cells. Ordinarily they do not "organize" or "determine" in any strict sense but, to speak figuratively, function as "go signals" for cells which otherwise might wait. Apparently, as cells of an embryonic system reach a certain stage of development they may give off substances which when added to the milieu of cells of another system enable the latter to differentiate according to their own intrinsic potentialities. In the absence of the

appropriate organizer the cells may remain undifferentiated or even follow some other course (as in potential lens tissue, Lewis[11], Stockard[6]). This is of great importance in embryogenesis and also throws light on a possible path of protoplasmic evolution.

From some points of view the vitamins have much in common with the hormones and organizers. The chief difference seems to be that the vitamins are synthesized outside the animal body, but it is not certain that this distinction is a very valid one.

## Inter-Relation of Factors

It is not the purpose here to do more than suggest that at least some of the vitamins are merely substances upon which protoplasm has become dependent through evolutionary adaptation, and that the hormones may be either rather complex vitamins which the body has evolved the capacity to synthesize, or metabolic components of the internal environment to which there have been evolutionary responses analogous to those elicited by factors in the external environment. That the whole problem of food, vitamins and endocrines can be reduced to really simple terms is quite unlikely, but there is good reason to think that there has been an interesting evolution of specialization with reference to hormones and vitamins as well as to other external factors. To cite but one example, some evidence might indicate that the estrogens which play such an important role in the mammalian reproductive cycle are phylogenetically older than the mammals themselves. Indeed it may be that they were first evolved by the plants, and the reason they are estrogens at all is inherent in the cyclic or seasonal character of plant growth. How much evolution there has been in the hormones since animals began to elaborate them for themselves is an interesting problem whose solution lies mostly in the future. Riddle[12] has made some very interesting contributions to this phase of the subject in his studies of prolactin.

When we attempt to evaluate all these diverse factors, we are led in each case to the cytoplasm as the reacting system. The cytoplasm is obviously adjusted to respond to influences which emanate from the genes within and the hormones, vitamins and similar factors from without.

## The Probable Evolution of Sex

One of the primary functions of sex is apparent to the geneticist who makes use of it in the improvement of domestic plants and animals. Sex

affords above all else a means for combining in one individual favorable traits from a variety of sources. If it were not for amphimixis, each desirable trait would be in conflict with every other good trait except in the rare cases where several favorable mutations chanced to occur in the same germ line. In the absence of sex, if favorable genes were to appear in different lines, they would only serve to increase the competition between those lines, with the probable extermination of some and the consequent loss of desirable genes. But under a system of sexual reproduction, germ lines which enjoy advantages due to favorable heredity are likely to be brought into contact with each other when, instead of being purely competitive, their good qualities may be combined by interbreeding and preserved and multiplied by natural selection. Sexuality, therefore, may be presumed to have had the effect of changing favorable mutations in different germ lines from necessary antagonists to potential synergists. Without sexual reproduction it is doubtful if the kind of protoplasm which early appeared in our world could ever have reached a differentiation much beyond that of the simpler plants and animals. There are, of course, other important aspects of sexuality, but the advantages alluded to would alone seem to offer sufficient reason for its evolution, once the function of conjugation had appeared.

Of the many kinds of sex that may have arisen among the Protista, it seems likely that the kind which gave rise to sex in the higher plants and animals, must at first have involved only the gametes. Botanists long ago pointed out what looks like a plausible sequence leading from zoospore to isogamous gametes, to heterogamous gametes and finally to the egg and sperm of oogamy (Allen[13]). The concomitant evolution of the soma seems to have been from plants or animals in which (a) any cell at all might break up into vegetative reproductive units or gametes, either isogamous or differing in sign, through (b) those in which only certain cells function in reproduction with the gradual evolution of special organs in which such cells can develop, to (c) the final segregation of two classes of individuals each of which suppresses the production of one or the other type of germ cells and so can function only as a male or a female. Briefly, it appears that sex started as a difference between germ cells and has evolved into a difference between individuals.

If we turn now to consider the conditions under which the morphological aspects of sex develop, a number of interesting features emerge.

In the first place, study of lower forms shows us that the kind of dimorphism exemplified by sex is not a unique phenomenon. It represents a rather common tendency toward what, to borrow a word from the bacteriologists, we might call pleomorphism. It is probably not essentially different from the dimorphism or polymorphism that results when individuals of some plant or animal species, if subjected to different environmental conditions, assume correspondingly diverse forms. Environmental factors in such cases are not necessarily directive in any sense other than that they act as "trigger mechanisms" to set off one or another train of possible reactions. When such responses fall in a continuous series, they excite no special interest, but when they are discontinuous, and especially when there is some suggestion of the "all-or-none", curiosity is aroused. That a plant is large when grown in rich soil and small when grown in poor soil is not particularly exciting, but if it has one kind of leaves in water and another on land, we are impressed.

Structural adaptation for the production of male or female germ cells seems to be merely one of these alternative responses, which may be conditioned by a variety of external factors. It is found to be so in an immense number of existing species where the genic constitution is such as to permit the reproductive tissues to develop indifferently into either an egg-producing or a sperm-producing organ. But in many species each new individual receives a set of genes with a differential bias in favor of one sex or the other. This is accomplished through the elaboration of the familiar XX-XY complexes. But such a differential as is established by an XX or an XY serves merely as one influence among the many to which the developing cytoplasm is adjusted to respond. There is little evidence that cytoplasm containing one of these chromosomal complexes is any more responsive to that particular complex than it would be to the alternative one. The sex-chromosome influence may be, and often is, outweighed by other internal or external factors. It is difficult to say whether in its evolutionary development the chromosomal control of sex has been perfected through an intensification or multiplication of the factors whose balance is determined by the XX and XY combinations, or by an increase in the sensitivity of protoplasm to those factors which already existed. A few illustrations will serve to emphasize how great are variations in the adequacy of the chromosomal regulation of sex differentiation.

## Chromosomal Differentiation

The differences between species strongly suggest an evolutionary sequence. In a vast array of lower animals each individual may produce either sperm or eggs, and we have learned something of the conditions which regulate these two types of activity. Two especially effective differentials are age and season. When sex is associated with season it may be mediated through some hormonal or prehormonal substance of the sort considered in the next section. But in all these cases where sex is conditioned by external factors it is clear that the potentialities of both sexes are inherent in each individual. Chromosomal determination is brought about through the intensification of differentials which were already present but so well balanced that the scale could be tipped only by some external factor.

The mollusks are particularly interesting in this connection. Many of them seem to be without a chromosomal bias in favor of either sex. For example, in some of the pteropods sperm and eggs may be seen developing almost simultaneously in the same gonad (Danforth[14]). Among bivalves the oyster, as Professor Coe[15] has pointed out, presents an interesting series of conditions indicating a range from no sex bias at all to a feeble tendency toward internal control, but almost always with a marked disposition to protandry. But of all the mollusks thus far described the gasteropod, *Ariolimax californicus*, is among the most interesting. In genetic and ecological studies of this species, C. C. Wright* has shown that chromosomally there are two sexes, XY males and XX females. The XY individuals apparently invariably function as male throughout life. The XX individuals, however, are protandrous, behaving as typical males during the early part of their life after which they lose their external copulatory organs and from then on behave as true females. In this species the chromosomal differential is obviously not quite strong enough in young individuals to overcome a widespread molluscan tendency to protandry, but it becomes wholly effective when the animal reaches full maturity.

Among the Amphibians, especially the Salientia, the chromosomal sex mechanism can be over-ridden fairly easily as many investigators have shown (e.g. Witschi[16], Burns[17]), and even among higher vertebrates we find evidence that chromosomal determination is not necessarily final. But there would be little ground for any suspicion that a

* *Stanford University Press Dissertations*, 1938-39.

chromosomal mechanism is intrinsically inadequate for sex control. Indeed, there is no reason to suppose that any extreme to which sexual dimorphism has thus far led could not have been regulated entirely by the chromosomes, as it still seems to be in some of the insects, with no need of any hormonal differentials whatever.

## Hormonal Differentiation

Purely intracellular regulation of function is not well adapted for coordination. To this defect we are probably largely indebted for development of the nervous and endocrine systems. In respect to the latter, some of the lower plants are rich in hints of possible evolutionary sequences. It has been known for a long time that among the algae there are certain, mostly periodic, environmental conditions that help to regulate the reproductive cycle. Various authors have gathered evidence that light in changing intensity, temperature, and especially substances dissolved in water may at times stimulate conjugation or gamete formation. But not all related species react in the same way to the same stimuli (Danforth[18]). That the factors on which a species depends for its stimulation should characteristically become effective at the very season which is best suited for the propagation of that particular species is probably not a mere coincidence. It may conceivably have come about by some chance fitness or preadaptation of the protoplasm to its environment. But it seems much more probable that favorable reactions were gradually evolved through protoplasmic alterations and natural selection, to the end that there have developed many kinds of protoplasm each adapted to respond to some particular set of environmental conditions. Perhaps adaptations at this really biochemical level may in fact constitute one of the most significant aspects of evolution, and one which may yet lend itself to precise analysis.

The recent studies of Moewus[19] on reproduction in *Chlamydomonas eugametos* seem to mark a step in this direction. He finds that in the proper media vegetatively reproducing plants without cilia can be propagated in the dark. Brought into the light such plants soon develop cilia and motile gametes. But even when left in the dark the cells may be made motile and reproductive by the addition of filtrates from cultures grown in the light. When such filtrates are added, one class of gametes, which may be called "female", is activated first, followed a little later by activation of the other class. The substance which is effective on

these cells is produced in an inactive form by cultures growing in red or orange light. When the filtrate from such cultures is subjected to blue or violet light it passes rather rapidly through a series of phases. First, after a few minutes of exposure, it acquires a capacity to activate "female" gametes, then it becomes inactive for a short time, followed by a brief period in which it activates "male" gametes, after which it remains completely and permanently inactive toward all gametes. Moewus[19] further reports that identical results may be obtained if, instead of the filtrate, a carotinoid, crocin, is added to Chlamydomonas cultures grown in the dark. Finally by mixing two crocin derivatives, each by itself inactive, either the female-stimulating or the male-stimulating substance can be obtained, depending on the proportions in which the two ingredients are combined.

Such manifestations are rather suggestive of the hormonal activity we see in higher forms. In Chlamydomonas they seem to approach a degree of chemical simplicity that permits one to hope they may ultimately become understandable. It is easy to imagine that in its evolutionary history Chlamydomonas protoplasm acquired the capacity to elaborate several crocin esters and then to react with them in such a way that gametes should be produced and activated at a time and in a manner that is advantageous for continuity of the species. How the chemical make-up of the protoplasm has become adjusted to give these reactions is by no means obvious. It is still more baffling that at reduction-division the contents of a single cell can so segregate as to give two cells, one of which will be activated by one mixture of chemicals, the other by a different mixture of the same chemicals. These are fascinating problems for those who can cope with them, and their solution is bound to do much to clarify our ideas of evolution. But in the meantime there is no justification for relinquishing the morphological approach or a point of view which permits us to look upon the development of function as "purposeful," in a biological sense.

Among the lower animals a number of species have been studied in which sex seems to be determined by environmental factors of a chemical nature. In the classic case of the worm Bonellia (Baltzer[20]), it seems that whenever an undifferentiated larva comes in contact with a female it becomes attached to her proboscis and develops as a small parasitic male. In the absence of an opportunity to indulge this particular tendency it becomes a female, except that a larva isolated *in vitro* may be made to

become a male or an intersex by adding much or little of an extract of female tissues, or even certain salts. We may suppose that instead of any mysterious potency in extracts of female Bonelliae, what is really demonstrated is an evolutionarily acquired adaptive capacity on the part of the larva to react in a characteristic way to certain conditions, if it meets them, and in another way, if it does not.

It would not be profitable in this connection to attempt to review all the evidence of hormonal regulation of sexual development and function in the lower forms[21], but it may be recalled in passing that if we are not too restrictive in our definitions, such regulation may be said to be of widespread occurrence. With some birds, such as the brown Leghorn fowl, certain characters seem to be almost completely under hormonal control. In laboratories where special experiments are being carried on with this breed, even a professional poultryman would find it exceedingly difficult, if not impossible, to determine the original sex of some of the birds on the basis of comb and plumage alone. Genetically male and genetically female Leghorns which have had their original gonads removed and then been subjected to the same kind of implants or injections come to be similar almost to the point of identity in some of their more conspicuous characteristics.

For the mammals there is an appreciable body of literature, familiar to this audience, indicating that among some of them too there may also be a considerable degree of equivalence in the capacity of male and female somatic tissues to respond to either male or female hormones.[22, 23] One need mention in this connection only such striking examples as the freemartin in cattle, "sex-reversals" in the guinea pig, changes resulting from parabiosis, and the intersexes of both genotypes which have recently been produced in mice and rats by injecting pregnant females with excessive amounts of male or female hormones (Hamilton and Gardner[24], Green and Ivy[25]). Moreover, the extraordinary interrelation of the mammalian pituitary and other glands concerned with reproduction, for a knowledge of which we are greatly indebted to the pioneer work of the president of this society, makes mammalian endocrinology a subject to tax the research capacity of the most gifted.

We can not yet infer how general or, in the case of some species such as man himself, just how complete hormonal determination may be (Dantchakoff[26], Raynaud[27]). But it is safe to say that there are mammals in which at least some traits may be fully conditioned by hormones,

and this almost irrespective of the initial chromosomal constitution.

And so we may conclude from this survey not only that it is entirely within the range of biological possibility for a high degree of sexual specialization and dimorphism to be determined by either a genic or an endocrine background, but that both types of determination are in fact realized[28]. For our present discussion it is immaterial whether the extracellular or "humoral" differentials are established by experimental means or result from the hereditary idiosyncrasies of some endocrine gland (Smith and MacDowell[29]). In either case it seems simplest to look upon the reaction as a matter of protoplasmic adjustment where the emphasis should be placed not on the stimuli but on the protoplasm which integrates and utilizes them. The prospect of an early and adequate analysis would be brighter if it were not for the fact that both modes of response have developed side by side in the same lines. This situation is clearly revealed by the types of plumage dimorphism in birds, which I would now like to discuss briefly as illustrative material.

## Genes and Endocrines in Relation to the Plumage of Birds

In studies on birds the conventional procedures involving removal of glands, with or without replacement therapy, injection of hormones, hybridization and skin transplantation have on the whole yielded harmonious results when applied to any one species or race, and often seemingly discordant results when applied to different species*. It may be worth while to review some of these results briefly, citing a few specific experiments.

There are certain characteristics which distinguish the feathers of each part of the body, but many transplantations of skin[31] from one part to another have resulted in no change in the character of the feathers produced. In some species a change of hormonal level will, and in others, will not affect the plumage, irrespective of whether or not transplantations have been done. Among a few of these strains genetically determined changes in the threshold of responsiveness to hormones are known to have occurred, and in all of them there are regional differences in responsiveness which have been acquired embryologically. Taken together they afford interesting parallelisms between "phylogenetically" and ontogenetically acquired differences. Transplantation of skin from one sex to the other yields especially illuminating results and shows what

* Domm[30] provides an excellent discussion and bibliography covering this field.

wide interspecific differences really exist.

A piece of skin transplanted at hatching from a male to a female dwarf turtle dove has for several years produced feathers indistinguishable in size and color from those of a male, and quite different from surrounding feathers from the female's own skin. Since the volume of the original transplant was less than that of one of the many feathers which it has since produced we may infer that there is no longer anything of significance in the graft except the genes and cytoplasm descended from those originally transplanted. It would seem that in this case the female produces no hormones whose actions differ, so far as the feathers are concerned, in any respect from those of the male. Injection and castration experiments in doves, pigeons, guinea fowl and a number of other species indicate that such lack of differential effects of male and female hormones on plumage characters is not an uncommon one. In this group, as in others, the very same hormones may or may not, according to the species, affect other secondary sex characters such as bill color or development of gonoducts.

When a transplant similar to that in the dove was made from a male to a female common pheasant[32], the feathers produced by the transplanted skin were different from those of either a male or a female, showing a kind of compromise both in color and in structure. With grafts made in the reciprocal direction, again a compromise was obtained, but one different from the first. In these pheasants we find four very distinct types of plumage corresponding to the four possible combinations of male and female hormone, male and female protoplasm and genes. This is true of several kinds of pheasants and, judging from the findings of Stadie[33], is probably also true of a number of the European songbirds.

When instead of the preceding species, brown Leghorn chicks were used for both donors and hosts, the feathers produced by each graft were like those of the host irrespective of the sex of the donor. In other words, the Leghorn is at the opposite extreme from the dove. In the dove sex differences in plumage are regulated by genes without reference to hormones, in the Leghorn they are regulated by hormones without reference to genes. If in adult Leghorns there are any traces of the genic effects seen in pheasants, they are at the very best only slight.

But there are other races of fowl in which the reactions are different. Various experiments in skin transplantation between Campines and Leg-

TABLE

GENIC AND HORMONAL FACTORS IN THE PRODUCTION OF PLUMAGE DIMORPHISM

| | | *Types of plumage in four different genotypes* | | | |
|---|---|---|---|---|---|
| *Chromosomes* | *Sex hormones* | *A* | *B* | *C* | *D* |
| WZ | F | 1 | 1 | 1 | 1 |
| ZZ | F | 4 | 2 | 1 | 1 |
| WZ | M | 1 | 3 | 1+ | 4 |
| ZZ | M | 4 | 4 | 2 | 4 |
| WZ | O | 1 | 3+ | 4— | 4 |
| ZZ | O | 4 | 4 | 4 | 4 |
| WZ | F+M | 1 | 1 | 1 | 1 |
| ZZ | F+M | 4 | 2 | 1 | 1 |

WZ, female, and ZZ, male sex; F, ovarian, M, testicular, and O, none. A, dove, guinea fowl and others; B, common pheasants such as Reeves, ring-neck and others; C, fowls of the Campine-Sebright group; D, fowls of the Phoenix breed and, approximately, the Leghorn-Plymouth Rock group. 1, female plumage; 4, male plumage; 2 and 3, intermediate plumage.

horns,[34] as well as exchange of gonad transplants and hormonal injections have shown that the Campine fowl has feather follicles whose threshold for hormonal stimuli are very different from those of the Leghorn. A Campine follicle can produce the same kind of feather as the corresponding Leghorn follicle, but it does so only under the influence of a quite different hormonal balance. From genetic evidence it appears that a single gene difference is responsible for the divergent reactions in these two races. The young of both these and other birds produce a series of juvenile feathers which seem to indicate a progressive adaptation to the hormonal or genic factors with which they will ultimately react more fully.

The table summarizes what might be characterized as four types of adult reaction between genes and hormones, or, better, four ways in which different forms of protoplasm respond to these internal and external factors. It is quite possible, indeed probable, that the arrangement in the table does not correspond to any particular evolutionary sequence, but it does show the kind of diversity which would seem to provide for evolution of special types of response. When it is recalled that the differences in reaction shown in columns C and D are due to but a single gene, it is not surprising that one finds diversity of response to be due

much more often to difference in tissues than to difference in hormones. As an example of this diversity it may be mentioned that all of the four types listed give their own individually characteristic responses to comparable doses of the same mammalian estrogen.

In addition to the experiments just mentioned, it has been found by chance that a much more delicate type of transplant is possible. This is because of the tendency of young pigmentoblast cells to wander, occasionally crossing the line between graft and host. This results in production of mosaic feathers which are found in most series of transplants and have been studied recently with great success by Willier and his colleagues[35]. In some of these mosaics where a few pigmentoblasts of one type may become relatively isolated in a foreign environment, the responses, or lack of them, are as characteristic as when there has been no operation at all. Again it seems to be the cells and not the hormones that determine the reactions.

Finally, when the humoral complex, which thus far has been considered as a unit, is analyzed with respect to its components, a still greater diversity is revealed. To cite only a single example, Professor Witschi[36] and later Doctor Stadie[33] found that, whereas in many species the pituitary stimulates the gonad and that in turn influences the feathers, there are some species (e.g. in the genus Pyromelanus) in which the follicles have acquired the ability to react directly with the gonadotropic hormone itself. This is precisely what might be expected to have happened on the basis of the general thesis that tissue-hormone reactions are in large measure determined by protoplasmic adaptations to already existing substances which happen to be present at the time when it is biologically desirable that the reaction take place.

## Summary

Experimental study of factors controlling sex differences in the plumage of birds has led to the conclusion that it is necessary to regard the hormones as essentially non-specific substances to which tissues of different species may or may not develop a capacity to respond. The situation found to exist in birds, and in other species of animals and plants as well, leads to the suggestion that one aspect of evolution may have involved a progressive adjustment of the cytoplasm to both intracellular and extracellular factors. It appears that the genes give character to the cytoplasm or "condition" it, while at the same time supplying substances

with which during development it becomes progressively adapted to react. Adaptations to hormones and organizers seem to be of much the same nature as those to genic effects. Apparently each new adjustment has come about primarily through a chromosomal alteration which imparted to the cytoplasm the capacity to utilize some substance already at hand.

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# CLINICAL AND PATHOLOGICAL ASPECTS OF ACUTE LEUKEMIA*

CLAUDE E. FORKNER

ACUTE LEUKEMIA is not a very rare disease. Its clinical diagnosis may be exceedingly difficult. Frequently acute leukemia must be considered in the differentiation of obscure disorders. It is the purpose of this address to review some of the important points with regard to the clinical, hematological, and histological characteristics of the disease.

Dr. Paul[14] has told you that the test for heterophile antibodies does not invariably distinguish infectious mononucleosis from acute leukemia. I think we can go still further and say that no procedure is available which will tell with certainty early in the course of illness whether a patient is suffering from acute leukemia or a leukemoid state. A number of disorders, some of them benign, may closely simulate and indeed at times be indistinguishable from acute leukemia. It must be within the experience of many of you to have seen patients in whom you have diagnosed acute leukemia and later, owing to the favorable outcome of the disease or to the acquisition of new data, have been gratified to witness your diagnostic error. The medical literature contains scores of references to such cases, often regarded as remissions or cures of the disease, but probably more correctly interpreted as leukemoid states or as secondary or symptomatic leukemia. This subject will receive further consideration later in my address.

## THE CLINICAL PICTURE OF ACUTE LEUKEMIA

The disease may occur at any age, in any race, and in either sex. Authentic cases of leukemia in newborn infants have been recorded. It is of interest that all of the leukemic newborn infants and young children have had non-leukemic parents, whereas infants born of leukemic parents, of which there are about fifty well-documented cases in the literature, have in no instance been afflicted with the disease.

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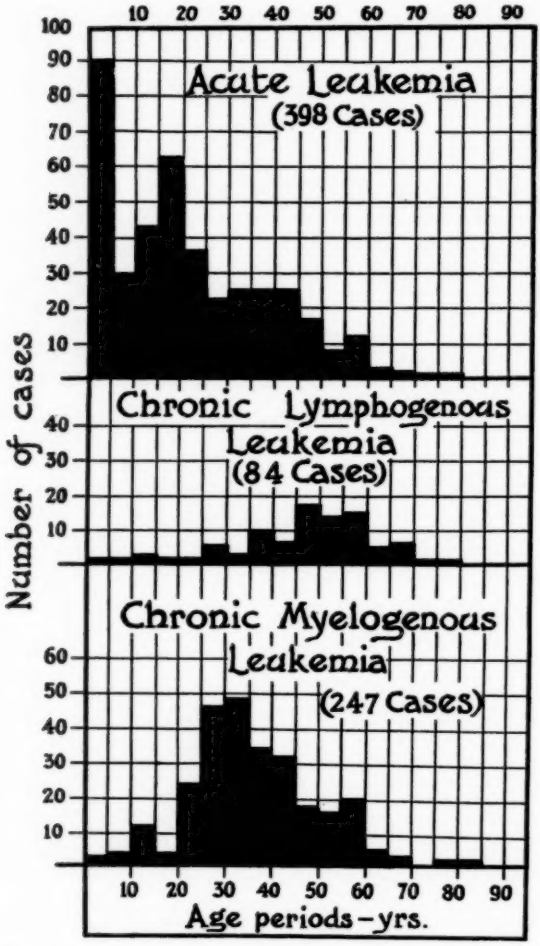


Fig. 1—The age incidence of three varieties of leukemia, arranged in periods of five years (Modified from the data of Ward[1]).

Figure 1 illustrates the age incidence of acute leukemia in relation to the age incidence of chronic forms of the disease. It is apparent that the acute disease has a tendency to occur at an earlier age than chronic leukemia. The graph is modified from that of Ward.[1] You will note that although rare, acute leukemia may occur at an advanced age. I

TABLE I

PROPORTION OF SEXES AT VARIOUS AGE PERIODS IN 929 CASES (WARD[1])

| *All ages to age of* | *Acute leukemia* | | *Chronic lymphemia* | | *Chronic myelemia* | |
|---|---|---|---|---|---|---|
| | *M.* | *F.* | *M.* | *F.* | *M.* | *F.* |
| 5 | 60 | 40 | — | — | — | — |
| 10 | 65 | 35 | — | — | — | — |
| 15 | 69 | 31 | 75 | 25 | 60 | 40 |
| 20 | 72 | 28 | 80 | 20 | 61 | 39 |
| 25 | 71 | 29 | 83 | 17 | 55 | 45 |
| 30 | 71 | 29 | 81 | 19 | 52 | 48 |
| 35 | 70 | 30 | 76 | 24 | 52 | 48 |
| 40 | 69 | 31 | 86 | 14 | 52 | 48 |
| 45 | 68 | 32 | 75 | 25 | 53 | 47 |
| 50 | 68 | 32 | 77 | 23 | 55 | 45 |
| 55 | 67 | 33 | 75 | 25 | 54 | 46 |
| 60 | 67 | 33 | 77 | 23 | 56 | 44 |
| 65 | — | — | 73 | 27 | 56 | 44 |
| 70 | — | — | 74 | 26 | 56 | 44 |
| 75 | — | — | 74 | 26 | 56 | 44 |
| 80 | — | — | 75 | 25 | 56 | 44 |
| 85 | — | — | — | — | 56 | 44 |

have myself observed a typical case supported by postmortem study in a man eighty years of age. Additional evidence was presented by Warren.[2]

Leukemia in all of its forms is more common in the male, but the course of the disease in the two sexes appears to differ in no important respects. Table I, taken from the data of Ward,[1] shows the sex incidence of acute and chronic leukemia at various ages. It will be noted that the preference for the male is not so marked in the earliest age group as in subsequent groups. These observations were confirmed in the studies of Minot and his associates.[3]

The onset of acute leukemia may be insidious or abrupt. In about 50 per cent of patients, the beginning of illness is like that of a respiratory infection, often with fever, sore throat, cough, and general malaise. The patient is thought to have catarrhal fever, grippe, influenza, or tonsillitis; but instead of prompt recovery, prostration persists; the patient continues to feel badly, to have fever; he develops pallor and a tendency to bleed from the mucous membranes and into the skin. Sometimes the

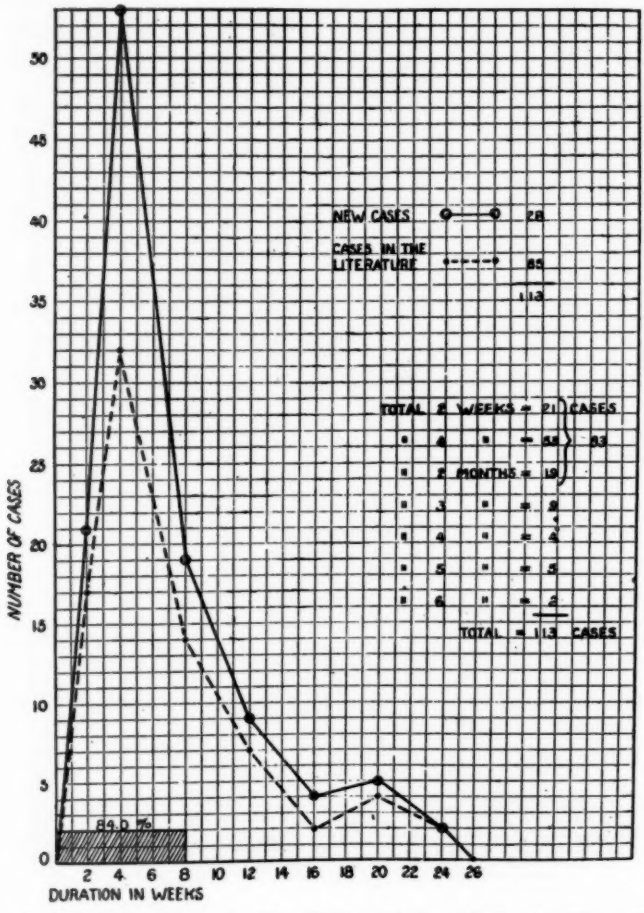


Fig. 2—Duration of illness on 113 patients with acute leukemia (Warren[3]).

onset, particularly in children with acute lymphocytic leukemia, simulates closely that of acute rheumatic fever, as has been stressed by Cooke,[4] Smith,[5] Sutton and Bosworth,[6] and others. Baldridge and Awe[7] found acute arthritis in thirteen of twenty patients under twenty-one years of age suffering from lymphocytic leukemia.

The onset of acute leukemia may be marked by bleeding from the gums or aching of the teeth so that the patient believes the origin of his trouble is a local disorder in the mouth. Such patients, before they are

seen by physicians, frequently consult dentists who may perform extractions or other operative procedures which are followed by uncontrollable hemorrhage, osteomyelitis of the jaw, or extension of an ulcerative process.

Among other symptoms which may appear early in the disease and which cause patients to seek medical advice are fever, tachycardia, enlargement of lymph nodes, weakness, disturbances of vision, and irregularities of menstruation. Early in the course of the disease no significant anemia may be present, but occasionally pallor, the result of anemia, may be the first manifestation which brings the patient to his physician.

As a rule, the steady progressive course of acute leukemia is unchecked either by natural agencies or as the result of treatment. A number of isolated instances of spontaneous remission and a few cases of apparent cure have been recorded. Warren[2] recorded the duration of the disease in 113 cases (Figure 2); ninety-three per cent of the patients died within two months and all within six months. The causes of death are varied. There may be terminal bronchopneumonia, septicemia, or hemorrhage. Agranulocytosis may precede death or occur at any phase of the disease. Severe prostration, myocardial failure, or progressive anemia may be precipitating causes of death.

Before proceeding with a discussion of the differentiation of the various types of acute leukemia, I wish to provide you with a simple classification of the leukemias (Table II) in order that you may be better oriented concerning the remarks to follow. Time does not permit that we consider this aspect of leukemia in detail, but the subject has been presented elsewhere by Forkner.[8,9] Leukemia, in general, is classified on the basis of whether it is acute or chronic, leukemic or subleukemic (aleukemic). Many workers prefer to indicate the site of origin of the cells which are concerned and to designate the types as myelogenous (myeloid or medullary) or lymphogenous (lymphoid or lymphatic). Other workers prefer to designate more specifically the strain of cells primarily involved. For example, one may speak of acute or chronic lymphocytic, monocytic, or eosinophilocytic leukemia. The fourth column in Table II gives a list of the specific types of acute or chronic leukemia which may be encountered. The more common types are indicated in capital letters. It is these types that I wish to discuss particularly.

TABLE II

CLASSIFICATION OF LEUKEMIA (LEUCEMIA, LEUKOSIS, LEUCOCYTHEMIA)

| CLINICAL DESIGNATION | GENERAL TYPE OF LEUKEMIA | CELL OF ORIGIN | SPECIFIC TYPE OF LEUKEMIA (Common types indicated in capital letters) | SYNONYMS DEPENDING ON COMMON USAGE, ON COURSE OF THE DISEASE OR ON CLINICAL OR HEMATOLOGIC CHARACTERISTICS |
|---|---|---|---|---|
| LEUKEMIA OR SUBLEUKEMIC (Aleukemic) LEUKEMIA (Acute or chronic) | Myelogenous (Arising from cells of bone-marrow) | Myeloblast | NEUTROPHILOCYTIC LEUKEMIA | Myelogenous, Myeloid, Myelocytic or Myeloblastic Leukemia. Myelosis |
| | | | Eosinophilocytic Leukemia | Eosinophilic Leukemia |
| | | | Basophilocytic Leukemia | Basophilic Leukemia |
| | | | Chloroleukemia | Chloroma or Chloroleukosarcoma |
| | | Myeloblast and Megaloblast | Erythroleukemia | Leukemia Associated with Erythremia |
| | | Megakaryoblast | Megakaryocytic Leukemia | |
| | Lymphogenous (Arising from cells of lymphoid tissue) | Lymphoblast | LYMPHOCYTIC LEUKEMIA | Lymphogenous, Lymphoid, Lymphatic or Lymphoblastic Leukemia, Lymphoblastoma Leukemicum, Lymphadenosis |
| | | | Leukosarcoma | Lymphosarcoma Associated with Leukemia |
| | Lymphogenous or Myelogenous | Primitive Mesenchyme Cell | Stem Cell Leukemia | Hemohistioblastic, Embryonal or Lymphoidocytic Leukemia |
| | | Plasma Cell Myeloblast Lymphoblast | Plasma Cell Leukemia | Plasmacytoma with Leukemia or Multiple Myeloma with Leukemia |
| | Disputed | Monoblast | MONOCYTIC LEUKEMIA | Histiocytic Leukemia, Reticulosis, Reticuloendotheliosis, Reticulum Cell Leukemia, Reticulosarcoma |

## The Differentiation of the Various Types of Acute Leukemia

Since acute leukemia is a fatal disease and cannot be treated satisfactorily by any known therapeutic agent, there exists the feeling among some physicians that attempts to subclassify the disease into various types of acute leukemia are not justifiable. This attitude, although it is the path of least resistance, does not advance knowledge of the disease, leads to the inadequate study of cases and hence confusion in the medical literature. Many of the textbooks of medicine and of the papers on leukemia state that all types of acute leukemia are identical in their symptoms, although it must be admitted that all patients with acute leukemia do not exhibit the same symptoms.

Another reason that acute leukemias often are not separated into their various subtypes is that to do so is difficult and has required exceedingly careful study of the blood cells by expert hematologists using all available methods. In the following remarks I shall stress certain important clinical signs which have been too little appreciated and which aid greatly in complementing and substantiating hematologic differentiation of types.

About four decades ago, Gilbert and Emile-Weil[10] distinguished three principal types of acute leukemia according to the prevalence of the main symptoms. Their first type was the rare but typical acute leukemia with enlargement of the lymphoid tissues as the predominant feature. Their second type was the hemorrhagic form characterized by an intense hemorrhagic diathesis. The third type described by these workers was the buccopharyngeal or the anginous and pseudoscorbutic form with hemorrhagic infiltrations and necrotic, ulcerative processes in the oropharyngeal cavity. These were purely clinical types and were not known at the time to be correlated with any hematologic criteria.

Working independently and without a knowledge of the earlier studies of Gilbert and Emile-Weil, I had the opportunity a few years ago, while working at the Thorndike Laboratory in Boston, to study intensively a considerable number of cases of acute myelogenous, acute lymphogenous, and acute monocytic leukemia. We were able by hematologic methods, confirmed by the study of pathologic specimens, to separate these three main types of acute leukemia. When these hematologic types were correlated with the clinical pictures it became apparent

that the buccopharyngeal or pseudoscorbutic type of Gilbert and Emile-Weil was, hematologically, acute monocytic leukemia; that their hemorrhagic form was, hematologically, acute myelogenous leukemia, and their type with enlargement of lymphoid tissues, was acute lymphocytic leukemia. On the basis of further studies we were able to formulate, even more completely, definite syndromes associated with the different types.

### Lesions of Mucous Membranes as an Aid in Differentiating Acute Leukemias

It was our opinion in 1934,[11] and this has been supported by subsequent observations, that diffuse marked swelling of the mucous membranes, particularly of the gingivae, usually with ulceration and necrosis, was characteristic of acute monocytic leukemia and usually was absent in acute leukemia of the lymphocytic or neutrophilocytic (myeloblastic) types. Frequently diffuse cellulitis with swelling and pain, together with signs of acute inflammation extending into the deeper tissues of the face, was present. Because of these presenting symptoms, patients often consulted their dentists prior to being seen by physicians. Patients with acute lymphogenous and acute myelogenous leukemia frequently have symptoms referable to the mouth and other mucous membranes, but in my experience these lesions usually are of a different sort and are limited to hemorrhages and slight infection.

### The Size of the Spleen and Lymph Nodes in Acute Leukemia

The spleen in acute myelogenous leukemia often is enlarged somewhat but usually it is not palpable; whereas in acute lymphogenous leukemia the spleen almost without exception is felt two or more centimeters below the costal margin. In acute monocytic leukemia the spleen is palpable in the majority of cases and may be conspicuously enlarged. In four of my cases the spleen at autopsy weighed from 360 to 1065 grams.

Almost invariably there is distinct general enlargement of the lypmh nodes in acute lymphogenous leukemia. In acute monocytic leukemia the lymph nodes, particularly those in the neck, may be slightly or moderately enlarged, but general enlargement to the extent found in acute lymphogenous leukemia is not present. It is even more uncommon to find generalized enlargement of lymph nodes in acute myelogenous

leukemia and, if any enlargement is found, it is slight in degree.

Because of these characteristic lesions of the mucous membranes, and of the spleen and the lymph nodes, which were closely correlated with hematologic and autopsy findings, it has become possible to make a satisfactory clinical differentiation of the acute leukemias even when the blood picture is not clear cut or when other tissues do not become available for histologic studies.

### Hematologic Differentiation of the Acute Leukemias

There are five important characteristics of the blood in acute leukemia: (1) The dominant leukocytes (usually over 80 per cent) are of uniform and immature type. There are exceptions to this general rule in certain cases of acute lymphocytic, acute monocytic, acute eosinophilocytic leukemia and chloroleukemia. In these latter disorders the cells may appear more mature and the leukocytes resemble those of the chronic rather than the acute disease. When a very large proportion of the leukocytes are myeloblasts, lymphoblasts, and monoblasts, there may be almost no intermediate stages in development. This renders difficult deductions as to the type cell by observation of intermediate phases in maturation. This difficulty is further accentuated by the fact that, owing to the greatly disorganized hematopoietic system, immature cells of other strains than that of the type cells may be present in moderate number in the blood. (2) A second characteristic of the blood in acute leukemia is that the total number of leukocytes may be subnormal, normal, or increased. Frequently the total number fluctuates widely. Leukopenia of a severe grade may be present at any phase of the disease and commonly is present in both acute myelogenous and acute lymphogenous leukemia near the time of onset of the disorder. (3) Blood platelets are markedly decreased, sometimes absent. Too little attention is directed in general medical clinics to observations of blood platelets and their variations. Study of these structural elements is of great importance in the differentiation of acute leukemia from many other diseases. They may contribute the most significant clue in a difficult diagnosis. Warning should be given, however, against accepting the results of routine direct enumeration of the platelets except when this is done by an expert and checked by examination of a good blood smear. (4) The coagulation and bleeding times usually are prolonged. (5) Anemia develops rapidly, although at the beginning of the disease, no significant anemia

may be present. Except when complicated by chronic loss of blood, the anemia is of the normocytic and normochromic type. Frequently, immature erythrocytes are present and the number of reticulocytes is increased.

The number of blast cells is frequently so large and the intermediate phases in maturation of the type cells are so few that it may be exceedingly difficult to determine whether the blast cells are myeloblasts, monoblasts, or lymphoblasts. Under these conditions some workers have classified the leukemia as being of the stem cell or embryonal cell type. On the other hand, careful study, at least in my experience, of cases regarded by others as stem cell leukemia, usually has demonstrated that the type cells belong to one of the three main strains, namely, myeloblasts, monoblasts, or lymphoblasts.

The "supravital" technique is of particular value in the differentiation of the monocytic strain of cells and aids materially in the recognition of early myelocytes and their immediate precursors, the myeloblasts. There are, moreover, certain finer distinctions in cell types which are present in ordinary Wright's stained smears. The nuclei of myeloblasts are large, round, oval or slightly indented and contain several nucleoli. The cytoplasm is deeply basophilic and uniform in character. The nuclei of monocytes, premonocytes, and monoblasts, for the most part, tend to have complicated shapes and possess very few nucleoli. The cytoplasm is relatively abundant, is generally not very basophilic, and contains many dust-like granules.

Another useful means in the differentiation of the various types of acute leukemia is the oxidase or peroxidase reaction. The shade of color and the size of the positive granules in monocytes are somewhat different from those in the myelocytes and myeloblasts. The size of these granules in monocytes usually is smaller and their number fewer than in myelocytes or so-called myeloblasts.

### Histologic Differentiation of the Acute Leukemias

Patients with acute leukemia in whom the hematologist has difficulty, likewise present distinct problems for the pathologist. It happens rather frequently that pathologists are in a less favorable position to make a precise diagnosis of the type of leukemia than are the internists. One of the chief criteria upon which the pathologist relies is the oxidase reaction of the tissues. If the cells infiltrating the liver, kidney, and other tissues

are oxidase positive and if the architecture of the blood-forming organs is disorganized and shows indiscriminate hyperplasia of uniformly immature leukocytes, the diagnosis of myelogenous leukemia is made. On the other hand, if such a state exists, but without a positive oxidase reaction, the diagnosis of lymphogenous leukemia or of lymphoblastoma is in order. With the discovery of a third type of leukemia, monocytic, the pathologic diagnosis became more difficult, because in this type the oxidase reaction of the blood and tissue cells may be either positive or negative and hence the chief point for the differential diagnosis is lost.

There are, however, certain characteristics of the histology which are of great importance, which are little appreciated, and which usually are distinctive. Although it is often extremely difficult or impossible in good paraffin sections to distinguish lymphoblasts from myeloblasts, this is not true of monocytes and their precursors. The monocytes, when observed by means of the oil immersion lens in the blood, or in their sites of formation in the tissues, have certain characteristics distinguishing them from myeloblasts or lymphoblasts. The nuclei, even of premonocytes and of monoblasts, usually are of irregular shape, often in the form of irregular crescents or of broad elongated bands bent on themselves. Frequently, the nucleus may be bent on itself several times giving the impression of lobulation. There exist also many young monocytes, the nuclei of which may be of simpler structure, but they exist as close companions of the cells with the more complicated nuclei. The nuclei of the monocytic series of cells rarely have demonstrable nucleoli, whereas these structures are common in lymphoblasts and are even more prevalent in myeloblasts. The cytoplasm of premonocytes and monoblasts as a rule is more abundant and much less basophilic than that of either lymphoblasts or myeloblasts.

A point of importance is the degree of infiltration and obliteration of the normal architecture of lymph nodes. It is well known that in lymphogenous leukemia the lymph nodes generally are overgrown by diffuse proliferation of lymphoid cells destroying the essential organization of the nodes. In myelogenous leukemia many lymph nodes may be involved with myelogenous leukemic infiltrations, but usually there is preservation of the architecture of the node. Now in acute monocytic leukemia the involvement of the lymph nodes histologically is conspicuous and of an intensity closely approximating that of lymphogenous leukemia. The essential architecture may be completely destroyed.

TABLE III

DIFFERENTIATION OF THE THREE MAIN TYPES OF ACUTE LEUKEMIA (FROM FORKNER[9])

| | | Acute Myelogenous Leukemia | Acute Lymphogenous Leukemia | Acute Monocytic Leukemia |
|---|---|---|---|---|
| Spleen | | Usually not palpable | Almost invariably significantly enlarged | Palpable in about 70 per cent of cases |
| Lymph nodes | | Usually slight or no enlargement | General enlargement of moderate or marked degree | Moderate in neck, but other lymph nodes very slightly enlarged, if at all |
| Liver | | Usually palpable | Usually palpable from 1 to 4 cm. below costal margin | Usually palpable from 1 to 4 cm. below costal margin |
| Mucous membranes, particularly of mouth and pharynx | | Petechiae, bleeding; often slight swelling of gingivae but rarely ulceration | Petechiae, bleeding; rarely ulceration | Petechiae, bleeding; usually marked, diffuse swelling of gingivae or pharynx with ulceration; often cellulitis with swelling and tenderness of face; marked fetor oris |
| Histologic distinctions of type cells in blood and tissues | Oxidase reaction | From few to many oxidase-positive cells, with from few to many coarse granules | All lymphoid cells oxidase-negative | All monocytes positive or all negative, or some positive and others negative; positive cells contain relatively few fine granules |
| | Other characteristics | Dominant cells myelocytes "A" (Sabin) and myeloblasts; nuclei round or oval, usually with several nucleoli; cytoplasm deeply basophilic; myelocytes "B" (Sabin) present; Auer's bodies frequently present in few cells | Dominant cells lymphoblasts and young lymphocytes; nuclei round, oval or slightly indented, with few nucleoli usually present; relatively small amount of deeply basophilic, hyaline cytoplasm; mature lymphocytes present in fair number; occasional myelocytes "C" (Sabin) and metamyelocytes present | Dominant cells monoblasts and premonocytes; nuclei usually elongated and folded deeply indented or otherwise irregular in contour; nucleoli rarely present; cytoplasm relatively abundant, usually not deeply basophilic and not hyaline but slightly basophilic and "ground glass-like"; Auer's bodies may be present in few cells; mature monocytes present in significant and varying numbers; myelocytes "C" and metamyelocytes often present in small numbers |

It is thus apparent from the preceding discussion that acute leukemia can be differentiated clinically, hematologically, and histologically into various types. By means of the accompanying Table III, I wish briefly to recapitulate the essential points in the differentiation of the three types of acute leukemia.

## Leukemoid States

There is one further point that demands consideration in any discussion of the acute leukemias. What are the diseases with which they may be confused, and how does one separate a so-called leukemoid state from a true leukemia? Infections of various sorts may produce clinical and hematologic pictures resembling closely or remotely those of acute leukemia. This has been so striking that some workers, for example Wallbach,[13] believe that a sharp borderline between infection and leukemia does not exist. In connection with this it should be stated that the possibility of leukemia of man being a virus disease is still open. The fact that considerable evidence suggests that leukemia is a neoplastic process has not settled the question and has done little to advance our knowledge with regard to its etiology.

Perhaps the disease with which acute leukemia is most easily confused is infectious mononucleosis. You have noted in the paper by Dr. Paul[14] a detailed presentation of the characteristics of this disease. In addition to the heterophile antibody test, there are other points which often distinguish the two disorders. Chief among these is the behavior of the blood platelets. Whereas in infectious mononucleosis the platelets are, as a rule, little if any affected; in acute leukemia, almost without exception, the platelets are greatly decreased. Associated with this, the tendency for spontaneous purpura or other hemorrhage is present in acute leukemia but usually absent in infectious mononucleosis. Often the degree of immaturity of the leukocytes is greater in acute leukemia than in infectious mononucleosis. The oxidase or peroxidase reaction, when positive in the immature cells, indicates that they are not lymphogenous in origin and so this test is of value in excluding infectious mononucleosis. In acute leukemia nucleated red blood cells are often found in the smear whereas this does not occur in uncomplicated infectious mononucleosis. Anemia develops rapidly in acute leukemia whereas in infectious mononucleosis this factor is not conspicuous. Biopsy of an enlarged lymph node may be useful in differential diagnosis but often this is not essential.

Acute disseminated miliary tuberculosis sometimes is associated with striking abnormalities in the blood picture with an outpouring of many immature leukocytes. In a number of instances the true diagnosis has been revealed only at autopsy. Roth,[15] Marshall,[16] Wiechmann,[17] Thompson,[18] and others have reported such cases.

Whooping cough, especially when complicated by bronchopneumonia may be associated with leukocyte counts of from 50,000 to 300,000 per c.mm. of which a high percentage (up to 90 per cent) may be lymphocytes. Acute leukemia, especially in children, may be accompanied by intractable cough associated with mediastinal masses. The differentiation of the two diseases may at times offer difficulties until close attention is given to the details of the blood picture.

Acute agranulocytic angina frequently is confused with acute leukemia. Indeed, acute agranulocytosis may occur as a complication in an otherwise frank case of either chronic or acute leukemia. In agranulocytic angina, 90 or even 100 per cent of the leukocytes present may be mononuclear forms. Many monocytes and a few myelocytes may be present at the beginning of the recovery phase. Unless one is cautious in interpreting such changes, they may be mistaken for manifestations of leukemia. Here again careful study of the details of the blood picture as well as a careful history, especially with regard to the taking of drugs, will lead to the correct interpretation.

Neoplasms, especially when the liver, spleen, lymph nodes, or bone marrow are involved by miliary metastases, may give rise to leukemoid blood pictures. Leukocytosis up to 140,000 per c.mm. and with the presence of many myelocytes, myeloblasts, and nucleated red corpuscles has been observed. The picture more often simulates that of chronic than acute leukemia.

Osteosclerosis, Hodgkin's disease, multiple myeloma, poisoning with chemicals, and infection with pyogenic organisms may at times be confused with acute or chronic leukemia.

## Treatment

Little has been said concerning this phase of the subject. No form of therapy provides any permanent relief. Transfusions of blood are of fleeting value. It is important, however, not to lose hope when one is treating such patients. Every effort must be expended in attempting to find some other explanation than leukemia for the altered state of the

patient. Although we cannot cure the disease, it is my belief that progress is being made and that sooner or later someone will discover the secrets which until now have remained hidden.

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# CHRONIC GASTRITIS: CLINICAL ASPECTS*

BURRILL B. CROHN

CHRONIC gastritis should be defined as a protracted inflammatory lesion involving one or more coats of the stomach wall, with a characteristic histological picture and gross pathological changes, with a typical or at least generally distinctive symptomatology and a known clinical course and progression. These criteria, while not necessarily constant, should be more or less uniform to deserve the appellation of a clinical entity.

The diagnosis of chronic gastritis was current perhaps a century ago, little understood and vaguely recognized. Its popularity was replaced by a functional or secretory phase of interpretation which was ushered in by Kussmaul with the introduction of the flexible stomach tube, and carried on by Ewald and Boas (1885) and more latterly by Rehfuss and his school of followers (1914). In more recent years the nervous (Leube) or functional or psychic explanation of gastric disorders replaced in public opinion all other causative and etiological explanations of symptoms relative to the epigastrium and, whether of cerebral or psychic or autonomic nervous system imbalance (Eppinger and Hess), achieved first place in clinical recognition.

With the application of the x-ray to gastrointestinal disease (1905) the pendulum swung to the opposite extreme, the effort being made to interpret most gastric phenomena from an organic viewpoint, particularly ulcer, ulcerations and duodenitis.

Today we are at the parting ways of a new concept, or at least of a revised or revived explanation of those gastric disorders of vague origin which, below the level of gross pathological recognition, call for clinical interpretation.

The invention of the ingenious and safe flexible gastroscope by Schindler has reopened this phase of investigation. With the introduction of this instrument and its capable use by experienced manipulators, a whole field of hitherto acceptable concepts has been reopened for re-

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From the Medical Services, The Mount Sinai Hospital, New York.

vision and renewed critical analysis.

One of the most important contributions of the gastroscopists has been the reawakening of our knowledge of gastritis. While surgeons, pathologists, and clinicians such as Konjetzny, Puhl, Henning, Gutzeit, Hurst and others have studied morphological gastritis in its relation to ulcer and carcinoma without arriving at more than debatable and uncertain conclusions, the gastroscopists have defined for us a gastritis which to them is a disease, not necessarily associated with other pathological changes; one with a clinical symptomatology which is offered to us as, in itself, an explanation of subjective phenomena and of visceral manifestations.

The gastroscopist sees with his instrument changes in the gastric mucosa which are real enough, of marked superficial congestion with edema, occasional hemorrhagic areas, surface erosions and increased mucus production. The process may be hyperplastic and productive in nature or may proceed to the stage of atrophy.

As old-school clinicians we are asked to accept these visualized pictures as representing a disease entity; as such, we ask, is there an associated recognizable clinical picture? Is there a corresponding histological change in the mucosa? Does the process lead to characteristic secretory changes? Can one diagnose or recognize or treat a case of chronic gastritis if one be deprived of the gastroscope and has to rely only on other diagnostic equipment?

Conceding gladly and ungrudgingly the surface changes seen through the flexible instrument, do these manifestations explain the pathological and clinical concept of a gastritis?

## Pathological Data

To what extent does histology of the stomach mucosa parallel the gastroscopic observations? The literature, extensive as it is, fails to answer this query. In fact, the dearth of studies on microscopic pathology is bemoaned by Henning, as well as by Schindler himself, both of whom express the hope that studies of this nature will in the near future be carried out by painstaking investigators. The real handicap lies in the fact that biopsies are not possible with the closed lens system of the flexible instrument; nevertheless, such studies are possible and are being carried out by a group at the Mt. Sinai Hospital who, having in a preliminary examination subjected the patient to a gastroscopy, now proceed

to a minute histological survey of the resected specimen, closely following such an examination.

Allowing for our modest inexperience in comparison with such a master gastroscopist as Schindler, and taking into consideration the fact that most of the cases were subjects of benign ulcers, we may still hazard a preliminary impression regarding the parallelism between the gastroscopic visual report and the histological analysis of the specimen.

In general such parallelism is inconstant. Frequently when hypertrophic, or less often, atrophic changes are seen with the gastroscope, but little morphological disturbances of structure are visible. Or, when a comparatively normal mucosa is seen, rather advanced infiltration with round cells and plasma cells and eosinophiles may be noted, even to polymorphonuclear invasion. In some instances the parallelism is good, a gastritis is seen grossly and an infiltrating congested mucosa is observed microscopically. In others, all parallelism is absent.

One of the greatest drawbacks in the whole issue is the lack of knowledge regarding what constitutes a normal mucosa, and what changes can be expected in the mucous membrane of individuals who are advanced into the later decades of life. Practically speaking, one rarely sees histologically a normal human mucosa without some cellular infiltration of the mucous membrane. Normal control specimens of mucosa are missing and slides devoid of some cellular hyperplasia or atrophy are to all intents and purposes absent. Some cellular changes characterized by round cell and plasma cell infiltration and connective tissue proliferation are commonly found in other viscera of the adult body, such as the appendix, liver, pancreas and kidney, and yet such changes are not regarded as coming within the realm of clinical consciousness.

By what yardstick are we to determine when a gastritis by microscopy is a gastritis by clinical definition? In the more advanced and severe grades of gastritis the gross specimen with its hyperplastic changes, marked thickenings, prominent gastric areas, even to the stage of *état mamelonné*, may be easily recognizable, as it is to the gastroscopist, and readily verified by the microscope as an advanced gastritis; but the less developed and subtler changes of the mild fundal and corpus gastritis may confuse the gross pathologist, as it may the gastroscopist. It is in these milder and less advanced instances that the histological verification may contradict the gastroscopist's findings.

## Secretory Changes

There are no consistent variations in the secretory titer that characterize the various forms of gastritis in their milder degrees. All writers agree that no form of gastritis, except the advanced type of atrophic gastritis with its associated achylia, has a pathognomonic change in the secretory acidity or in its morphological constituents (Simpson[1]). We have similarly failed to find a hyperacidity or a hypoacidity that can be predicated upon either the gastroscopic picture of a gastritis or upon a histological change in the cellular arrangement of the mucosa. Not that such a microscopic picture must be demonstrable to parallel secretory variations, but the difficulty of drawing up a clinical syndrome is enhanced by the absence of consistent findings in either the gastroscopic or the histologic picture and the presence of wide variations in the secretory composition.

## X-Ray Evidence

The radiographic evidence of gastritis is similarly confusing. The hypertrophied rugae demonstrable in the mucosal pattern of some stomachs are not a consistent sign of hyperplastic gastritis; nor are the prominent gastric areas and mottling demonstrated by Berg[2] and by Henning and Schatzki,[3] nor the worm-like arrangement of the antral rugae of Gutzeit[4] sufficiently convincing to allow one to draw the conclusion of the presence or absence of a mucosal gastritis. By general agreement (Schindler and Templeton,[5] Henning,[6] Schloss, Ettinger and Pratt[7]), radiography unsupported by gastroscopy is inadequate to determine the presence of a gastritis.

On what basis then may one formulate a clinical picture of gastritis? If histological control norms are absent, if the changes in the microscopic morphology do not consistently parallel the observed gastroscopic findings, if no secretory or radiographic picture characterizes the disease, then only the gastroscopic picture and the subjective complaints of the patient remain upon which to build. A clinical syndrome that demarcates gastritis is concededly absent; the various other forms of chronic gastritis are said to be accompanied by epigastric pain, worse after meals, the absence of night-pain, nausea, vomiting, occasional hematemesis due to surface erosions, and general symptoms such as dizziness, vertigo, weakness, loss of appetite and of weight. A characteristic sensitive area has been described by Schindler[8] in the left periumbilical area as character-

izing hypertrophic gastritis.

Such symptoms are not mild, but are severe to a degree, and must be correlated as effect to cause with the gastroscopic picture. Beaumont,[9] whose opportunity and genius were unexcelled, says: "Diseased appearances similar to those mentioned above, have frequently presented themselves in the course of my experiments and examinations. . . . These morbid changes and conditions are however seldom indicated by any ordinary symptoms or particular sensations described or complained of, unless when in considerable excess or when there have been corresponding symptoms of a general affection of the system." Eusterman[10] clearly states that changes in the mucosa do not give rise to clinical symptoms, except occasionally epigastric distress or hemorrhage, thus differing with both Knud Faber[11] and Henning.[12]

If one could dispense with the demand for a histological basis of a disease, as well as with the secretory and roentgenological evidence of a process, one might be willing to interpret the gastroscopic picture in the light of a functional, rather than an organic disturbance. A subpathological entity gives rise to a subclinical picture, in which mucus production, severe congestion even to hemorrhages and motor spasm of long duration eventually lead to cellular changes. Similar disturbances in the nature of pathological physiology characterize some very severe diseases, such as mucous colitis, or chronic rhinitis, or allergic manifestations; diseases with well defined symptomatology, with minimal mucosal changes, but which eventually may lead to mucosal hypertrophy, polypoid formations or atrophic sclerosis.

The constant association of gastritic changes with nervous phenomena such as dizziness, depression, weakness, sense of fullness and insomnia might lead one to invoke a psychogenic or a neurologic factor as the responsible causative agency. Such nervous influences might well induce pathological disturbances of physiology to so great an extent as to produce functional and hyperemic congestive states in the stomach, which would be evident instrumentally but yet not produce organic mucosal changes.

Certainly the theory of Knud Faber[11] who attributed gastritis to previous general infections such as diphtheria, influenza or tuberculosis is hardly a convincing hypothesis, nor has it received general credence. If hasty eating, bad dentures, excessive quantity of ailments and too hot or too cold foods are the proper causative factors, then gastritis is or

should be the most common disease from which all of us suffer, which of course gastroscopically appears to be the fact. In truth, Gutzeit[4] said long ago that gastritis is the most universal of human ailments.

## Recognizable Forms of Gastritis

The difficulty with drawing up a clinical picture that will fit into the pattern of chronic gastroscopic gastritis should by now be evident. But, doubt as one may the significance of the interpretation of what one sees instrumentally, certain well defined and advanced forms of gastritis deserve very definite consideration.

The association of the so-called giant rugae on the greater curvature of the stomach with hypertrophic gastritis has received much attention. The gross crenelation of the border of the greater curvature simulating an early neoplastic defect, the distortion and erasure of the outermost folds and the undue prominence and exaggeration of the lateral and longitudinal folds of the fundus and corpus have frequently been interpreted as being based upon a hyperplastic gastritis with edema, congestion and broadening of the base of the folds as evidence of a disease process. This picture has been dealt with by Kantor,[13] Forssell,[14] L. G. Cole[15] and others. It is truly a very confusing radiographic phenomenon; one which requires accurate knowledge and interpretation to prevent the mistake, either of operating upon a supposed carcinomatous defect of the greater curvature, or of failing to explore a positive and deserving case on the hypothesis that the defect is to be interpreted as a chronic hyperplastic gastritis.

We have had experience with eight such cases, in which the symptoms consisted of abdominal distress, epigastric pain, anorexia, loss of weight and occasionally even a severe anemia. The course was usually a short one of a few months or years which, associated with the greater curvature defect and the exaggerated folds, cleverly simulated a neoplastic infiltration. Six of these cases were operated upon and explored. In three instances the greater curvature wall was reported as thickened or diffusely indurated; in three others the stomach was normal by palpation. Fortunately biopsies were taken in the first three instances in an attempt to define the underlying pathological process. On inspection at the operating table the mucosa appeared cobblestone in appearance; huge cerebriform gyri were present, the rugae thickened, mucosa not abnormal in appearance. The histological appearance of the three

TABLE I

GIANT RUGAE – SO-CALLED HYPERTROPHIC GASTRITIS

| NO | NAME | AGE | HISTORY | ACIDITY | X-RAY | OPERATIVE FINDINGS | HISTO-PATHOLOGY |
|---|---|---|---|---|---|---|---|
| 1 | E.S. | 72 F | 4 yrs. abdominal distress | 15-44 | 4 yrs. persistent filling defect greater curvature | Thickening entire wall; cerebriform Gyri | Mild, superficial Gastritis |
| 2 | M.D. | 50 F | 4 months nausea, weakness, vertigo | — | Inconstant Filling defect greater curvature | Thickened wall gr curvature, cobble-stone mucosa | Hypertrophic Gastritis |
| 3 | A.M. | 39 M | Epigastric pain | — | Shallow irregular defect greater curvature | Diffuse thickening entire wall, Rugae indurated | Superficial Gastritis |
| 4 | D.D.P. | 51 M | Anorexia, epigastric distress, loss of weight, 3 mos. | 40-70 | Filling defect greater curvature | Stomach normal by palpation | No biopsy |
| 5 | R.M. | 59 F | 1 yr. epigastric distress | — | Filling defect greater curvature and antrum | " " " | " " |
| 6 | H.S. | 60 F | 6 wks. cachexia, pallor High. 50% | — | Large filling defect near fundus, greater curvature | " " " | " " |
| 7 | A.S. | 61 F | Several years indigestion No pain | 0-16 | Prominent Rugae, gr curvature | No operation | well |
| 8 | M.E. | 38 M | 6 mos epigastric oppression, vomiting | 0-12 | Numerous transparencies resembling polypoid changes | " " | " |

biopsy specimens, taken through the entire wall of the suspected area, disclosed superficial gastritis in two instances and a hypertrophic gastritis in the third. There was no evidence of neoplasm nor of polypoid formation. The gastritic changes were of moderate intensity and the cellular infiltration of such degree and kind as might be found in any specimen taken from the mucosa of an adult individual used as a control. It is unlikely that the mucosal cellular changes accounted for the heaped-up cerebriform giant rugae appearance. The explanation of Forssell suffices better and explains its appearance. In his careful studies he was able to demonstrate such variations in the size and pattern of mucosal folds as could only be attributed to states of tonicity and contractility of the muscularis mucosae. The activity and spasticity of the muscularis mucosae determined, in his opinion, the form and depth and thickness of the mucosal folds or rugae; the pattern is variable and inconstant.

This variability may be clearly outlined in one of our cases in which, upon comparing three radiographs of the greater curvature taken at very short intervals, it is clear that the consistent defect of a neoplasm is absent and that the three films, upon comparison, show a diversity of pattern that can only be explained on the basis of overactive muscular contractility.

TABLE II

**ANTRAL GASTRITIS – SIMULATING ULCER**

| NO. | NAME | AGE | HISTORY | ACIDITY | X-RAY | GASTROSCOPY | OPERATIVE FINDINGS | HISTO-PATHOLOGY |
|---|---|---|---|---|---|---|---|---|
| 1 | L.R. | 37 M | One year pain, anorexia, gross hemorrhage | 72–92 | Numerous polypoid transparencies antrum | none | Cobblestone mucosa no evidence of ulcer | Polypoid Gastritis |
| 2 | F.G. | 60 F | 6 weeks pain heartburn anorexia | 60-90 | Mucous membrane markings increased | Edematous mucosa, congested single superficial ulceration | none | none |
| 3 | W.J. | 42 M | 10 years pain 8 months increased severity | 80-102 | Prominent mucosal pattern | Congestion, three superficial ulceration -healing observed | none | none |
| 4 | E.C. | 41 M | Occasional gas + pain, epigastric discomfort alcaholism | 66-80 | Marked increase folds, antral deformity and spasm | | none | |

Unfortunately, these cases all preceded the availability of a gastroscope, for in this field the gastroscope is supreme and serves a final purpose in eliminating the diagnosis of neoplasm. The gastritis in itself is an insufficient explanation of the phenomena since it involves only the surface mucosal areas and does not infiltrate the rugae, nor cause muscular thickening or cicatricial infiltration.

## ANTRAL GASTRITIS

Of all the clinical concepts of chronic gastritis, there is one which is consistent and clear-cut, one with a characteristic symptomatology, a positive gastroscopic picture, a definite radiographic pattern and a known clinical course—this is antral gastritis. Konjetzny,[16] Henning,[12] Eusterman,[10] Benedict,[17] and Golden,[18] have amply recognized and described this entity, so that any doubt of its acceptance is long since past. Its recognition is however laggard and need for appreciation of its outstanding characteristics calls for more general indoctrination.

Antral gastritis (Table II), of which we have closely studied nine cases, occurs at any period between thirty-five and sixty-seven years of age and is characterized by a diffuse hypertrophic and atrophic gastritis involving one or all the coats of the antrum and pylorus. The

mucosa is in general thickened and hyperplastic, often to the point of actual polypoid formation, the polyp or polyps projecting from a broad base simulating a neoplastic degeneration.

At other localities, areas of atrophic mucosa are seen representing an end stage of atrophic gastritis. The surface of the rugal folds may show superficial minute erosions or larger discrete ulcerations with rounded overhanging edges which, with the gastroscope, appear turgid and congested and easily friable. The submucosa is often enormously thickened like that of a linitis plastica; the muscularis propria is hypertrophied to a width several times its normal depth and resembles the benign hypertrophic pyloric stenosis described in the literature (Boas,[19] Konjetzny,[16] Cruveilhier[20]).

Histologically, the mucosal thickness which is normally 1.2 to 1.4 millimeters in cross-section may be two or more times that diameter, so that with the submucosal and muscular hypertrophy the whole simulates a new growth or a pyloric hypertrophy of organic origin.

The symptoms which accompany so definite a pathological process are equally definite. They simulate the picture of a benign ulceration of the prepyloric or antral region, only the gastroscope or an exploratory operation being capable of differentiating the conflicting symptoms. Pain and heartburn are the outstanding features in the ulcer-like cases; nausea and vomiting and weight loss those of the carcinoma-like instances. The epigastric distress and pain with anorexia and heartburn are usually more continuous than in ulcer; periodicity is lacking; the course is more rapid and severe and the general loss of weight and strength, more significant.

High normal or hyperacid secretory curves accompany the ulcer type. The gastroscopic examination usually shows an edematous, thickened mucosa, marked congestion, single or multiple superficial ulcerations with occasional deep penetrating Dieulafoy type of erosion. Healing of these ulcerations may be observed at successive gastroscopies. In one patient resection was done under the mistaken impression that he had a neoplasm. The mucosa when seen grossly was cobblestone in appearance and resembled the mottled areas described by Schatzki with spot radiographic films. Histologically a diffuse polypoid infiltrating gastritis of all the walls of the antrum was seen (Figures 1 and 2).

In these cases radiography is usually insufficient to differentiate these benign from potentially malignant conditions; an antral defect is per-

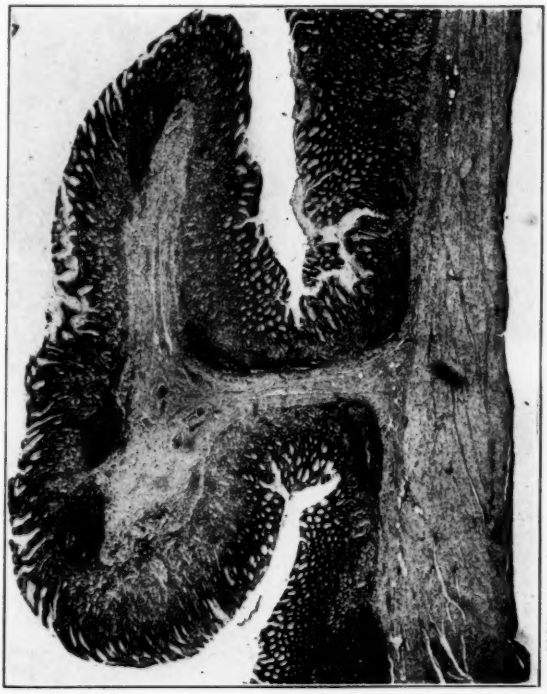

Fig. 1—Polypoid antral gastritis.

sistent and repeatedly demonstrable, the presence of the severe gastritis and of deep erosions throwing the antrum into spasm simulating a neoplastic defect.[18]

The type of case resembling from its initiation the picture of an antral tumor, as described by Flörcken,[21] is still more confusing (Table III). In this group anorexia, vomiting, epigastric discomfort and a rapid and severe loss of weight are alarming and progressive features. The course is one of months rather than years. Anacidity is the rule, though two of the five cases had low normal titers. Hematemesis and melena occur, though infrequently, as seen in the literature (Benedict[17]); one of our cases showed gross bleeding. The vomiting may well simulate that of true pyloric stenosis due to a cicatrizing duodenal ulcer. The hypertrophy of the pyloric and antral musculature is sufficiently obvious in the resected

Fig. 2—Severe atrophic gastritis with intestinal metaplasia of the surface epithelium.

specimen to explain the persistent emesis (Figure 3). Radiography demonstrates a filling defect of the antrum with prepyloric narrowing, lengthening of the pyloric canal (Kirklin and Harris[22]), infiltration of lesser and greater curvatures of the antrum and occasionally a true polyp formation as evidenced by an enduring luminosity or area of lesser density in one spot of the antral wall.

All of the five patients were subjected to resection under the impression of malignancy, all of them in the pregastroscopy days. The gross specimens showed marked and tumor-like thickening of the antral walls, polypoid mucosal hypertrophies, and a rigid thickened pylorus.

The etiology of antral gastritis is not clear. Alcohol cannot be indicted, nor do nutritional factors, faulty dentition, previous infections

Fig. 3—Antral gastritis with marked hypertrophy of the pylorus.

TABLE III

ANTRAL GASTRITIS—SIMULATING CARCINOMA- RESECTIONS

| NO. | NAME | AGE | HISTORY | ACIDITY | X-RAY | OPERATIVE FINDINGS | HISTO-PATHOLOGY |
|---|---|---|---|---|---|---|---|
| 1 | S.B. | 67 F | 5 months vomiting, loss weight | 0-10 | Filling defect, lesser curvature antrum | Gross Thickening antral wall serpiginous ulcerations | Atrophic Gastritis, erosions, thickening of submucosa and muscularis |
| 2 | H.S. | 57 F | 3 months anorexia, vomiting | 0-12 | Antral defect | Marked thickening of wall, polypoid mucosal hypertrophy | Severe acute and chronic Gastritis |
| 3 | H.O. | 45 F | 3 weeks nausea, epigastric discomfort | 16-48 | Prepyloric narrowing | Thickened pyloris, antrum 3 times normal | Chronic Gastritis, edema of submucosa, tremendous hypertrophy of muscularis |
| 4 | M.R. | 56 F | 2 months anorexia, nausea vomiting - loss 10 pounds | 26-46 | Prepyloric irregularity | Tumor-like thickening antrum, cobblestone mucosa | Chronic Gastritis, atrophy of glands, tremendous hypertrophy of muscularis |
| 5 | L.K. | 35 M | 4 yrs. nausea, vomiting | 0-8 | Prepyloric constricting lesion, Gastroscopy-polypoid gastritis | Cobblestone mucosa, small polyp. | Severe acute and chronic atrophic Gastritis |

nor unhygienic eating habits seem to be sufficiently unusual or potent to give rise to so severe a lesion. In spite of its severity, the course and prognosis of antral gastritis is relatively benign. The ulcer-like cases react well to restricted modified Sippy diet and alkalies, together with bed rest and change of habits of life. Rest and recreation are essential. We have used no gastric lavage though Hurst is enthusiastic about the employment of dilute hydrogen peroxide. Various bland medicaments have been recommended by others. The recognition of the disease process clarifies the problem. Here one leans most heavily on the gastroscopist, for on him falls the task and responsibility of differentiating the benign from the malignant and of outlining the therapeutic schedule.

Presumably even in the benign cases with polypoid formation and pyloric hypertrophy and stenosis, resection will at times become essential. Perhaps, with more popular and universal use of the gastroscope, earlier recognition of the cases will obviate extensive surgical procedure.

## Conclusions

We have observed that the gastroscopic picture of a chronic gastritis with difficulty is associated with any known histological change in the mucosa; and that secretory and radiographic diagnostic features are missing. Only with hesitation may we draw upon a clinical symptomatology that will express in pathognomonic or even suggestive manner the meaning of hyperplasias and atrophies seen through the flexible instrument. Yet, in its advanced stages we recognize with facility a type of antral gastritis that is well defined; that has clear-cut though not distinguishing characteristics; a persistent radiographic defect; and often secretory deficiencies.

Is this latter picture the end-stage of all those less well-defined appearances that the gastroscopist terms chronic gastritis? Or, is that which he sees merely a pathological deviation of function that is subclinical and lacking in a true morphological substratum?

For decades no clinician has ventured the clinical diagnosis of chronic gastritis. Today, a gastroscopist as well-known as Gutzeit declares that gastritis is probably the most common disease of mankind. The transition is too radical and extreme to permit such a reversal of all previous concepts without deliberate and cautious study, not only by the instrumentalist but by the body of observing physicians and pathologists.

Let us ask more time and more experience so that, with sound judg-

ment, we may recognize the outstanding features of a clinical syndrome and its course and progress before we formulate conclusions regarding the significance of these visual observations. At the same time, the recognition of the well-defined end-picture of antral gastritis, with its medical and surgical and diagnostic difficulties, calls for further research, more education and a greater diffusion of the knowledge derived from this study. Throughout, we depend upon the gastroscopist, for in his vision and perspicacity, and in the correct reporting and interpretation of his findings lies the future of the subject.

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# VITAMIN A
## WITH SPECIAL REFERENCE TO THERAPY*

ARTHUR M. YUDKIN

A CRITICAL REVIEW of the advancement of science reveals the startling fact that the knowledge of nutrition has played an important role in the development of modern medicine. At no period in the history of science has the progress of medical knowledge been so swift as in the last quarter of a century. The valuable contributions from the laboratories of Osborn and Mendel[1] and McCollum and Davis[2] were among the first in the present era of vitamin therapy. Their contributions inspired other laboratory workers who in turn helped implant more firmly the idea that diseases may be due to dietary deficiencies.

It was not until the fundamentals of an adequate diet were demonstrated that a relationship between faulty diet and the so-called deficiency diseases could be demonstrated. When the more important clinical manifestations of the disturbance are present it is not difficult to diagnose a deficiency disease.

It seems almost unbelievable that this condition should prevail in the United States where it seems reasonable to believe that the majority of the people receive enough of the food accessory factors in their daily diet to ward off a vitamin deficiency. Nevertheless, we are confronted with reports of borderline cases or subclinical states of dietary deficiencies. It is possible that these conditions are more readily detected because of the better understanding of the subject and because of their similarity to some of the disturbances produced experimentally in the laboratory animal by deficient diets.[3] It has also been observed that qualitative and quantitative errors in the diet frequently play a tremendous part in the etiology of human illness. It is noteworthy that vitamin deficiency occurs in all ages and is not confined to the poor classes but can and does occur even in prosperous communities.

To the clinician it may seem rather improper to interpret the afflictions of the human body largely in terms of pathologic findings observed

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From the Section of Ophthalmology, Department of Surgery, Yale University School of Medicine

in laboratory animals on special deficiency diets; but to one who has had the privilege of practicing medicine and participating in laboratory experimentation as well, it is understandable that use be made of this method of comparison. It is not altogether satisfactory from a scientific point of view to study large groups of people subsisting on poor diets, for under ordinary circumstances a diet deficient in one vitamin is likely to be unbalanced with regard to other vitamins, minerals, and basic food factors. It therefore became necessary to resort to experimental investigation for this knowledge.

Sufficient experimental evidence is at hand to warrant the conclusion that vitamin A is very essential for the maintenance of a satisfactory state of nutrition, normal growth, and health at all ages. Furthermore, Sherman[4] and his co-workers have reported that frequently a proportion of vitamin A in the food, sufficient to support normal growth and maintain every appearance of good health for a long time, may still be insufficient to meet the added nutritive demands of successful reproduction and lactation. Such observations as these emphasize to the clinician and student of nutrition alike the importance of ascertaining what constitutes the optimal intake of the various dietary essentials under all conditions of life. There should be greater emphasis placed on the optimum as contrasted with a merely satisfactory diet. Evidently a diet may be satisfactory, yet fail in some measure to meet the needs of the organism.

## The Nature, Physiology and Sources of Vitamin A

From the early experience with vitamin A and the substances having a vitamin A effect it was noted that several forms of precursors must be present in nature.[5] Foods having a yellow or green color are generally rich sources of this vitamin. In plants the vitamin activity was traced to the presence of carotinoid pigments. These pigments seem to be closely associated with chlorophyll in plant life. It has been shown that the quantity of chlorophyll may be considered as an index of carotene content of green plants. It was also observed that natural yellow color may be a rough qualitative guide for the selection of vitamin A active animal products, for it seems to indicate the consumption of carotenoids and vitamin A precursors by the animals. If the animal is capable of transforming carotene to vitamin A, the fatty animal products are apt to contain some vitamin A regardless of the color of the product; some

products may even be exceptionally rich in vitamin A and relatively poor in pigment. Certain of the fish liver oils have this characteristic, notably that of the halibut and the burbot.

Vegetable carotene is usually present in nature as a mixture of several forms. These have been classified as alpha, beta, and gamma carotene. The only other substance found to behave like the carotenes in acting as a precursor of vitamin A is cryptoxanthin. The carotene which seems to bear the closest chemical and biochemical relation to vitamin A is the beta isomer. The chemist tells us that it is a nitrogen free, alphatic, methylated polyene having two identical, unsaturated, methylated terminal rings. By comparing the formula for vitamin A with that for beta carotene it may be pointed out that the one molecule of beta carotene gives rise to two molecules of the primary alcohol vitamin A. In spite of the accumulated circumstantial evidence pointing to its actual chemical configuration, it is still important for science that the natural vitamin A be isolated in pure form and made available for clinical use. There are some recent reports[6] indicating that this has been accomplished but as yet they have not been confirmed. Similarly the conversion of carotene to vitamin A has not yet been accomplished by chemical procedures. *In vivo*, however, the liver is accredited as the site for the formation of vitamin A in animals but the detail of the process has not been elucidated.

It is known that a considerable amount of the ingested carotene appears in the blood and is deposited in the adipose tissue of man and animal. It has also been shown that after carotene is absorbed into the thoracic duct it is found in the liver. When a colloidal aqueous suspension of carotene is injected into the portal or systemic circulation, it is rapidly removed from the blood stream by the reticulo-endothelial system. It has been suggested[7] that the liver cells are necessary for the conversion of carotene to vitamin A by the fact that the conversion is decreased by phosphorus poisoning;[8] and in certain diseases of cattle which involve the parenchymal cells, carotene remains unconverted in large quantities in the Kupffer cells. It is known that vitamin A may disappear from the blood during starvation and during infection, even though considerable stores may remain in the liver.

According to Clausen[9] the vitamin A of natural oils and fats occurs as an ester; in preparations made by saponification it occurs as a free alcohol. When the vitamin was administered as a free alcohol it was found in the lymph mainly in the esterified condition. It therefore appears

that the mechanism of absorption of vitamin A includes linkage with fatty acids probably in the intestinal wall. Such linkage is impossible in the case of the hydrocarbon carotene, a fact which may explain its lower coefficient power of absorption. There is evidence that the vitamin is absorbed as a bile acid compound, transported in the blood and lymph as a fatty acid ester, and stored in the liver as a similar compound. This suggests that the vitamin performs its biochemical function in chemical combination with other substances rather than as a free substance.

Vitamin A and its precursors exhibit characteristic differences in absorption from the intestinal tract and certain physiologic conditions have been reported which alter the utilization of vitamin A and its carotene precursors. It is known that bile is essential for the utilization of carotene but apparently not for the utilization of vitamin A, for if bile is shunted from the small intestine to the colon, the utilization of carotene is prevented. It has been shown that liquid petrolatum does not interfere markedly with absorption of vitamin A from the intestine but does inhibit the absorption of carotene. The composition of the diet other than its vitamin A content, has been reported to affect the absorption and utilization of both vitamin A and the precursors called provitamin A. Absorption and utilization of vitamin A and carotene are affected by the quantity administered and the manner of administration, and the general physiologic conditions of the alimentary tract.

## Storage of Vitamin A in the Body

Experimentally it has been shown that most animals have a remarkable capacity for the storage of vitamin A. It is rather significant that most of the accumulated vitamin A in the body is present in the liver and small amounts appear in the lungs and the kidneys. It has been estimated that the vitamin A concentration of the liver of man, the rat, and cow on a normal intake is from 10 to 20 mg. per hundred grams. The vitamin A content is much lower in the liver at birth than in the liver of the normal adult. Thus it would seem that the accumulation of vitamin A in the liver tends to increase with age. The amount present is dependent on the character of the diet. The surprisingly low reserve of vitamin A in the newborn makes plain the necessity for an adequate intake of vitamin A during infancy.

The rat may in a few days store enough vitamin A to supply its nutritional requirements for several months. In times of low intake this store

is used to supply physiologic needs. It has been noted that during a prolonged deficiency the reserve is gradually depleted, normal cell functions are suspended, and pathologic change develops. Chronic diseases and infections seem to lead to slightly lowered vitamin A reserve. It is assumed that this takes place because of reduced intake of vitamin A or of decreased assimilation in the alimentary tract and increased metabolic demands.

## The Stability of Vitamin A and Carotene

Then the question arises as to the stability of these vitamin A values. It has been amply demonstrated that the physiologic activity of both vitamin A and carotene may be rapidly destroyed at high temperatures when oxygen or an oxidizing agent is present. According to Eddy and Dalldorf[10] the stability of any source of vitamin A will depend on the exposure of the vitamin or provitamin to oxidizing factors, to the presence or the absence of protecting factors, such as anti-oxidants in the holding source, or to the skill of the manufacturer in avoiding the action of oxidation in the preparation and merchandising of the vitamin sources. Practically all plant sources and animal sources show progressive destruction of the vitamin A during storage unless measures are taken to prevent fermentation and oxidation. Frozen products, however, seem to retain their vitamin A value well, whereas dehydration may be destructive to vitamin A unless quick drying to inactivate enzymes is utilized to prevent the destruction. Heat treatment in ordinary cooking operations appears to destroy little of the vitamin A value, perhaps because the carotene is less labile in plant tissues than is vitamin A itself. It is not readily affected at the ordinary temperatures of boiling and baking but is destroyed at high temperatures such as those obtained in frying. It is said that the destruction of vitamins is less when foods are heated at high temperatures for short periods than when they are heated at low temperatures for long periods. Although vitamin A is only slightly soluble in water, only small quantities of water or no water at all should be used in cooking. Steaming is one of the preferred methods for cooking, since the time required is short and the amount of water used is small.

## Experimental Observations

It is evident from the early animal experimentation that there must be some relation between vitamin A deficiency and poor dark-adaptation

of the eyes.[11] At first it was difficult to understand what part vitamin A played in the process until it was disclosed that the rate of regeneration of visual purple after its bleaching by a bright light in the living animal was less in the rats receiving the deficient diet than in the controls.[12] Pathological changes were observed at the chorioretinal junction (layer of Brücke) of the eyes removed from these animals.[13] It was shown that the fat extracted from normal retinae (of several species) is one of the richest sources of vitamin A substances.[14, 15] This finding suggested the possible relation of the vitamin A content of the retina and visual purple. Wald[16] succeeded in demonstrating in animals, birds, and amphibians that vitamin A was the prevailing substance in the extracted material of the retina. He also observed that visual purple on bleaching yielded a carotenoid which he called retinene. Retinene under certain conditions changed slowly to vitamin A and more rapidly to visual purple. On the basis of these observations Wald developed an equation which sets forth certain speculations on the chemical reactions which might take place in the rod and cone layer of the retina during dark-adaptation after the ocular tissue had been previously exposed to light.

A similar observation was made by Kühne[17] some sixty years ago when he noted that the visual purple in rat and rabbit retinae may be synthesized in two ways – a slow process in which the visual purple was developed from newly supplied materials, and a more rapid one in which the photoproducts of the stimulated retina were the starting point. Until recently the variation of the visual threshold in dark-adapted eyes was attributed to changes in the rods alone, but Hecht and his co-workers[18] demonstrated that the cones likewise play a significant role in this visual cycle. They conclude[19] from a study of thirteen persons afflicted with chronic liver disease that there is a true parallelism in the behavior of cone and rod thresholds in dark-adaptation and its response to vitamin A therapy.

A survey of old records reveals the frequent association of ocular diseases with famines caused by drought or war. Ophthalmologists have repeatedly attributed night blindness or hemeralopia, xerophthalmia, corneal lesions and several forms of chorioretinitis to faulty nutrition. These eye disturbances in man result from conditions so complicated that it is not possible without further evidence to attribute all of them to a specific starvation of a single vitamin. However, outspoken vitamin A deficiency in man appears to have been somewhat more common in

Europe and Asia than in this country. Recent studies in the United States would seem to indicate a surprising prevalence of subclinical vitamin A deficiency, particularly among children.[20] The diagnosis is based on the assumption that individuals who show poor dark-adaptation have a vitamin A deficiency.

Dark-adaptation is the change in light sensitivity which the eye undergoes in the dark following a stay in the light. It is an established clinical experience that hemeralopia may occur in poorly nourished persons and that great mental or physical exertion and exposure to glaring light may bring on the condition or aggravate an existing hemeralopia. Since dark-adaptation is mainly a phenomenon of rod and somewhat of cone function and is associated with the regeneration of visual purple, investigators have applied various means for the measurement of the rate of dark-adaptation to the problem of estimating vitamin A requirements of human beings.

These several methods which were recently described in special articles in the Journal of the American Medical Association[21] involve a principle which is common to all, namely, the measurement of the power of the eyes to adapt themselves to dim illumination. Some of these instruments are very simple while others are too complicated to be applied in routine clinical examination. As yet no one instrument fulfills all the necessary refinements for the measurement of dark-adaptation in people of all ages.

Clinical experience leads me to believe that there are several factors which may influence dark-adaptation; for instance, using the fundus oculi as a criterion, true light complexioned individuals (blonds) seem to have a different norm from that of the dark complexioned individuals (brunets); prolonged dark-adaptation is present in a variety of diseases; e.g., retinitis pigmentosa, retinitis albescens, choroideremia, glaucoma, and many others. It is important to point out that night-blind persons show poor dark-adaptation but poor dark-adaptation does not signify night blindness. In the latter instance the poor dark-adaptation comes on after exposing the retina to bright light. This is probably the condition that we are dealing with in vitamin A deficiency. There is another type of retinal disturbance which is called "glare-blindness," a condition which is often considered as nyctalopia in contrast to the condition of poor adaptation to dark known as hemeralopia. This also has been alluded to as a vitamin A deficiency.

## Clinical Observations

Vitamin A deficiency is practically unknown in nurslings; nevertheless, when the mother suffers from malnutrition, the nursling will also present manifestations of deficiency disease. The usual history of this type of disturbance reveals that the infant has been fed on a diet containing either insufficient milk, prepared milk, or no milk products at all over a period of at least one or two months; in many instances a digestive disorder may precede the onset of symptoms resulting in a diminished food intake together with imperfect absorption of the food consumed. Simultaneously there is a failure to gain in weight, and this may be followed by an actual weight loss. The normal activity of the child is diminished. The skin may become dry and scaly. In older children the eyes may show a viscid, stringy conjunctival secretion, matting the lids together. When the discharge is removed the cornea is clear and the conjunctiva is not congested. There is present, a marked photophobia and blepharospasm which is aggravated by exposure to light. As the condition progresses, a dryness of the bulbar and palpebral conjunctiva takes place with a typical Bitot's plaque adherent to the exposed conjunctiva of the eyeball. The cornea may now show small single or multiple ulcers which, if unchecked, go on to perforation of the cornea. Sooner or later hypopyon may result. In older children the eye condition often does not progress beyond a xerosis conjunctivae, and corneal destruction is less frequent even with a long period of vitamin starvation. In infancy the course of the disease is more rapid. This may be due to the greater need of the vitamin for growth. As the disease progresses, intercurrent infections of the skin, lungs, and urinary tract may occur, and finally the condition may terminate in bronchopneumonia or a diarrheal disorder.

Characteristic lesions of the human skin have been attributed to vitamin A deficiency. The lesions usually occur in sexually mature persons between sixteen and thirty years of age. They are much more frequent in men than in women. The disturbance appears first on the anterolateral surface of the thighs and posterolateral portion of the upper forearm and later spreads to the adjacent areas of the skin. The lesion consists of small pigmented papules at the site of the hair follicles. At first they appear as papules with keratitic plugs; later some of them develop into pustules. The skin is dry and scaly. Atrophy of the sweat glands and keratinizing metaplasia of their ducts are responsible for the

condition. There is a general increase in the pigmentation of the skin.

It has been suggested that gastric ulcers may be associated with vitamin A deficiency, but this condition is rather rare in the laboratory animals and in man. Likewise it has been said that diets deficient in vitamin A may cause urinary calculi. This assumption was based on the presence of urinary stones in experimental animals deficient in vitamin A and D and unbalanced in mineral content. This finding has not been corroborated by most investigators. Clausen[9] points out that although urinary calculi may be produced in experimental animals by feeding special diets, the factors involved are not yet clearly defined.

Although the vaginal mucous membrane becomes permanently cornified in animals deprived of vitamin A and the vaginal smear may be used as a method for the detection of the deficiency, the effects of moderate deficiency of vitamin A on fertility in man are unknown. Bessey and Wolbach[7] however, believe that atrophy of the testes and keratinizing metaplasia of the uterine mucosa may be expected in human adults.

## Prophylaxis

It is apparent that the prevention of A-avitaminosis depends upon two factors: the supplying of a sufficient quantity of vitamin A in the diet of the individual and the proper absorption of this factor. How much vitamin A is necessary for the maintenance of normal growth and health in the individual? We have as yet insufficient knowledge of the amount of vitamin A in the diet requisite for health. However, several investigators have made measurements of the minima for different species of laboratory animals and these might be regarded as offering suggestion. Cowgill[22] suggests that at least 400 international units per 100 calories per day is necessary for a child. This is based on the consideration of the maximum amount of vitamin A ever found in human milk and the idea that this might be nature's suggestion of an appropriate intake for the infant. This would lead one to assume that the ordinary diet contains sufficient vitamin A when cow's milk, butter, eggs, and certain vegetables and fruits are included. One must remember, however, that cow's milk may have a seasonal variation in its vitamin content dependent upon the diet of the cow. Since cow's milk runs about one-tenth to one-quarter of vitamin A value as compared with human milk, and cow's milk is the chief component given babies, it is obvious that there is justification of feeding vitamin A to the infant. The administration of one to two tea-

spoonfuls of standard cod-liver oil daily, will amply protect against any vitamin A deficiency no matter what the child's diet.

Harris[23] placed the minimal daily requirement at 1,000 units (U.S.P.). Jeghers[24] estimated that 4,000 international units of vitamin A daily represents the minimal requirement for a healthy adult. Growing children should be allowed twice this amount. Cameron[25] advised an optional intake of 5,000 units. According to Guilbert, Miller and Hughes[26] a level of vitamin A or carotene intake which is just sufficient to prevent gross signs of hemeralopia suffices also for excellent gains in weight and for maintenance of a thrifty physical appearance of animals for indefinite periods, although the storage of the vitamin in the body may be very meager indeed. These workers report that several species of animals (cattle, sheep, and swine) differing widely in body weight showed almost identical requirements for vitamin A or carotene per kilogram of body weight for the prevention of hemeralopia.

It is estimated that the foods recommended by the Health Committee of the League of Nations[27] would approximate a daily intake of 2,000 to 4,000 units for an adult and at least 5,000 U.S.P. or international units of vitamin A for the pregnant and nursing woman and 6,000 to 8,000 units of vitamin A daily for growing children.

The mere recital of these many figures emphasizes the fact that we are becoming reasonably quantitative in our approach to this problem. There may be some disagreement as to the exact requirement, but time will no doubt resolve this controversy. Inasmuch as the vitamin appears to be nontoxic, the clinician need not be unduly concerned if he chooses to give doses well above even the highest estimates just cited.

## Treatment

Obviously two lines of therapy suggest themselves: (1) the use of a high vitamin A diet, and (2) the administration of the concentrates or the pure substance in large doses. Inasmuch as the relief of deficiency symptoms seems quite definitely related to the amount of the needed factor supplied, up to the ability of the organism to utilize the vitamin, it is evident that the use of a high vitamin diet is of value chiefly in prophylaxis and in support of other therapy. It would probably be impossible to give the most effective therapeutic dosage simply by feeding an excellent diet. The use of various concentrates and the pure vitamin, when it becomes available, is definitely indicated therefore when marked symp-

toms of vitamin A deficiency appear. Patients suffering from this deficiency disease should be treated with a form of vitamin A that can be completely utilized. When cod-liver oil or other fish oils are not tolerated their concentrates are valuable. Some clinicians use carotene in these cases. In urgent cases where the digestion will not tolerate these substances, it is possible to administer vitamin A by an intramuscular injection of a cod-liver oil concentrate or the pure substance when it becomes available. In the advanced cases which occur so frequently in infancy, the digestion is often disordered and this must be treated carefully in order to allow the proper absorption of the vitamin A administered.

## Summary

It is apparent that vitamin A is a dietary essential, that conditions due to the lack of it occur and that these may be treated by numerous available sources of the vitamin. An attempt has been made to point out the limitations of the present knowledge concerning these conditions and their treatment. Although great progress has been made, with a continuation of research, we may confidently look forward to greater advances in our knowledge in this field.

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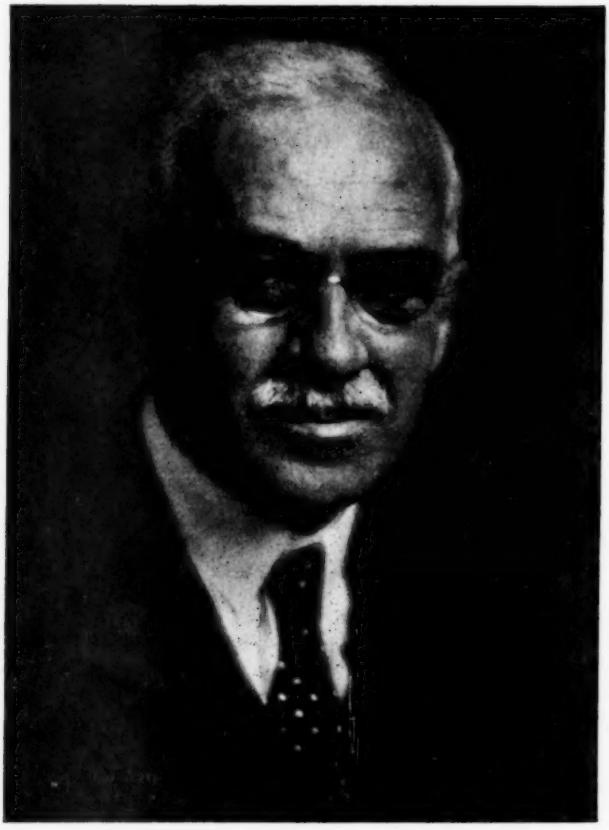

WILLIAM HALLOCK PARK

# IN MEMORIAM

## William Hallock Park
## 1863-1939

With the death of Dr. William Hallock Park on April 6, there has passed from us a lovable, distinguished and modest scientist whose work in the solution of major health problems brought incalculable benefits to mankind, and shed luster on American medicine.

Born in West Eleventh Street on December 30, 1863, the son of Rufus Park and Mary Hallock Park, Dr. Park's entire life was spent in and bound up with New York City and its institutions. At the age of twenty he graduated from the College of the City of New York; three years later he received the degree of Doctor of Medicine from the College of Physicians and Surgeons. Then came an internship at the Roosevelt Hospital, and postgraduate study in Vienna.

On his return from abroad, a modest scholarship placed at his disposal by Professor Prudden enabled Dr. Park to undertake a bacteriological study of diphtheria, a study which led to his entrance into the newly established diagnostic laboratory of the Health Department, April 1893. Here Dr. Park introduced the serum culture outfits for making throat cultures, a method still used throughout the world. Following the favorable reports concerning the newly discovered antitoxin for diphtheria, Dr. Park by the end of 1894 began producing the first antitoxin made outside of Europe.

Realizing that Dr. Park was far too valuable a scientist to keep at routine bacteriological work, Dr. Hermann Michael Biggs in 1895 established a Research Laboratory, in quarters over the disinfecting station adjoining the Willard Parker Hospital on East Sixteenth Street, and placed Dr. Park in charge.

In the same year the University and Bellevue Hospital Medical College appointed Dr. Park "instructor in contagious diseases." Thus began that notable career in teaching which during the next forty-two years influenced thousands of physicians who received their training at that famous medical school, and many other thousands of students who used Dr. Park's text book in their study of bacteriology.

Dr. Park thus held two positions and did a splendid job in each. In the health department, his direction of the Research Laboratory quickly made it one of the foremost institutions of its kind, while at the medical school he built up an outstanding department of bacteriology and hygiene of which by 1900 he was full professor. In 1933 his title was changed to Biggs Professor of Preventive Medicine and Director of the Bacteriological Laboratory, in which position Dr. Park continued until his retirement in 1937.

In 1901, when the New York County Medical Society organized its commission to supervise the production of "certified milk," Dr. Park was placed in charge of the laboratory work and field inspection. This marked his entrance into the field of milk sanitation, in which he quickly became the recognized authority. Moreover, as head of the Health Department Laboratories, the experience thus gained with certified milk made Dr. Park an invaluable adviser to the Department of Health in its efforts to provide safe milk for New York City.

One often hears efficiency experts say that one cannot hold two jobs at once and do them well. Dr. Park's career shows that he always filled more than two and that each contributed to the accomplishment of the other. His teaching at the medical college was undoubtedly better, more practical and more applicable because of his connection with the Health Department; his experience at the College certainly fitted him better to devise means whereby the Health Department could more effectively aid physicians in their work; his experience on the Regents' Board of Medical Examiners helped both medical schools and health departments in planning for the teaching of public health and preventive medicine; his connection with

the Certified Milk Commission was of inestimable value alike to physicians, to health authorities and to the milk industry; and finally his prestige as a scientist encouraged financial support of public health and medical education.

Dr. Park's laboratory at East Sixteenth Street was the Mecca of scientists from all over the world. And no wonder, for, figuratively speaking, there were no doors to his laboratory. Visitors were always welcome and were never denied the opportunity to observe the work and methods employed; no one went away without having received help and inspiration.

It is impossible in this brief memoir to indicate the enormous influence which Dr. Park's work had in the many fields in which he was active. Diphtheria, typhoid fever, dysentery, tuberculosis, pneumonia, meningitis, rabies, serum concentration, milk sanitation and pasteurization—these are a few of the subjects to which his laboratory made major contributions. Throughout all of Dr. Park's work one notes the accuracy and scrupulous honesty in reporting observations, and the insistence of adequate controls for all experimental investigations.

The best and truest memorial to Dr. Park is his accomplishment for humanity; and this we may visualize rather as a living and continuing influence and inspiration than solely the fulfilment of a noble life.

CHARLES F. BOLDUAN.

## *DEATHS OF FELLOWS*

EDGAR, JAMES CLIFTON: Round Hill Road, Greenwich, Connecticut; born in New York City, June 14, 1859; died in Greenwich, Connecticut, April 8, 1939; received from Lafayette College the degrees of Ph.B. in 1882 and A.M. in 1884; graduated in medicine from New York University Medical College of New York City in 1885; elected a Fellow of the Academy February 6, 1890.

Dr. Edgar was emeritus professor of obstetrics at Cornell University Medical College, consulting obstetrician to Bellevue Hospital and obstetrician to the Manhattan Maternity Hospital and Dispensary. He was a Fellow of the American College of Surgeons, a member of the American Medical Association, the American Gynecological Society, the New York Obstetrical Society and the State and County Medical Societies.

Dr. Edgar was the author of a notable book on the practice of obstetrics, and contributed many articles to the literature of his special field.

KENYON, JAMES HENRY: 563 Park Avenue, New York City; born in Cannonsville, New York, July 9, 1872; died in New York City, April 10, 1939; received the degree of B.S. from Princeton University in 1894; graduated in medicine from the College of Physicians and Surgeons, New York City, in 1898; elected a Fellow of the Academy May 5, 1904.

Dr. Kenyon was surgeon to Fordham Hospital, consulting surgeon to Booth Memorial and associate surgeon to the New York Neurological Institute. He was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the American Association for Thoracic Surgery, the New York Surgical Society and the County and State Medical Societies.

PARK, WILLIAM HALLOCK: 333 East 68 Street, New York City; born in New York City, December 30, 1863; died in New York City, April 6, 1939; received the degree of A.B. from the College of the City of New York in 1883; graduated in medicine from

the College of Physicians and Surgeons in New York in 1886; awarded the degrees of LL.D from Queens University, Kingston, Canada, in 1910, and D.Sc. from New York University in 1926, Yale University in 1929 and Columbia University in 1929; elected a Fellow of the Academy April 7, 1892. He was Vice-President of the Academy in 1927, 1928 and 1929.

Dr. Park was professor of bacteriology and hygiene at New York University and Bellevue Hospital Medical College, 1897-1937; director of the New York Public Health Department, Bureau of Laboratories, 1894-1937, and its director emeritus since 1937; consulting bacteriologist to the State Department of Health since 1914, and its medical examiner in bacteriology since 1917; consulting bacteriologist to the United States Quarantine Service since 1921 and consulting bacteriologist to the Willard Parker Hospital since 1931.

Dr. Park was a Fellow of the American Medical Association, a member of the American Public Health Association and its president in 1923, the Association of American Physicians, the American Association of Pathologists and Bacteriologists, the American Society for Experimental Pathology, and the County and State Medical Societies.

He was the author of a number of books on bacteriology and immunology and a contributor to technical journals on these subjects.

STOCKARD, CHARLES RUPERT: 1300 York Avenue, New York City; born in Washington County, Mississippi, February 27, 1879; died in New York City April 7, 1939; received the degrees of B.S. and M.S. from the Mississippi Agricultural and Mechanical College in 1899, and 1901; Ph.D. from Columbia University, New York City, in 1906; and D.Sc. from the University of Cincinnati in 1920; graduated in medicine from the University of Würzburg, Bavaria, in 1922; elected a Fellow of the Academy January 2, 1913.

Dr. Stockard joined the Department of Anatomy of Cornell Medical College in 1906, becoming professor of anatomy in 1911, a position which he held until his death. He was also President of the Board of the Rockefeller Institute of Medical Research and conducted cancer research for the Huntington Fund.

Dr. Stockard was well known as a lecturer, and among many others delivered the following: the DeLamar Lecture at Johns Hopkins University in 1925; the Harrington Lecture at the University of Buffalo in 1926; the Beaumont Foundation Lecture at Detroit in 1927; the Lane Lecture at Stanford in 1930; the Potter Memorial Lecture at Jefferson Medical College in 1934; and the Joseph Collins Lecture at the Academy of Medicine in 1937.

He was a member of the American Association for the Advancement of Science, the Society of Experimental Medicine and Biology, the National Academy of Sciences, and the American Association of Anatomists, secretary, 1914-22, and its president, 1928-30.

Dr. Stockard was the author of a number of books and contributed to many scientific journals. His chief investigations have been on subjects of morphology.

WASHTON, JACOB: 940 Grand Concourse, Bronx, New York; born in Russia, September 20, 1889; died in Sarasota, Florida, March 18, 1939; graduated in medicine from New York University and Bellevue Hospital Medical College in 1913; elected a Fellow of the Academy February 3, 1931.

During the World War, Dr. Washton served as a major in the American Expeditionary Force. His decorations included the British Military Cross and the French Legion of Honor.

Dr. Washton was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

# *TWELFTH GRADUATE FORTNIGHT*

## OCTOBER 23 TO NOVEMBER 3, 1939

## "THE ENDOCRINE GLANDS AND THEIR DISORDERS"

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### *The Program Comprises*

AFTERNOON CLINICS, EVENING MEETINGS, MORNING ROUND TABLE CONFERENCES, AND SCIENTIFIC EXHIBITS

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### EVENING SESSIONS

**The subjects and speakers at the evening meetings at the Academy will include:**

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| *Historical sketch of the development of endocrinology* | Herbert M. Evans |
| *Physiology of anterior lobe of pituitary gland* | J. B. Collip |
| *Pituitary hypothalamic syndromes* | Leopold Lichtwitz |
| *Hypo and hyperpituitarism* | Leo M. Davidoff |
| *Therapeutic application of female sex hormones* | Elmer L. Sevringhaus |
| *Physiology and principal inter-relations of the thyroid* | David Marine |
| *Hypothyroidism* | J. H. Means |
| *Hyperthyroidism* | Harold Thomas Hyman |
| *Surgical treatment of hyperthyroidism and other diseases of the thyroid* | Frank H. Lahey |
| *The adrenal medulla* | Walter B. Cannon |
| *Adrenal insufficiency* | Robert F. Loeb |
| *The adrenal cortex* | C. N. H. Long |
| *The Cushing syndrome. Neoplasms of the adrenal gland* | B. S. Oppenheimer |
| *Overfunction of the adrenal cortex* | Hugh H. Young |
| *Relation of diabetes to the endocrine system* | Rollin T. Woodyatt |
| *The influence of the central nervous system upon endocrine activity* | J. F. Fulton |
| *Physiology and pathology of parathyroids* | William G. MacCallum |
| *Hyperparathyroidism* | Henry L. Jaffe |
| *Physiology of the ovaries* | Philip E. Smith |
| *Physiology of testes and therapeutic application of male sex hormones* | Carl R. Moore |
| *Puberty, menstruation and pregnancy* | Robert T. Frank |
| *Menopause* | Ephraim Shorr |

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